IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HERON THERAPEUTICS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 22-985 (WCB)
	)	
FRESENIUS KABI USA, LLC,	)	
	)	
Defendant.	)	

HERON'S OPENING POST-TRIAL BRIEF

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Table of Abbreviations

ABBREVIATION	MEANING	EXHIBIT NO.
’229 patent	U.S. Patent No. 9,561,229	JTX-1
’794 patent	U.S. Patent No. 9,974,794	JTX-7
AC	Doxorubicin/Cyclophosphamide	
Agarwal	Agarwal et al., Process Optimisation, Characterisation and Evaluation of Resveratrol-Phospholipid Complexes Using Box-Behnken Statistical Design, 3 INT’L CURRENT PHARMACEUTICAL J. 301 (2014)	JTX-67
ANDA	Abbreviated New Drug Application	
Asserted claims	Claims 9, 10, and 21 of the ’229 patent and claims 9 and 10 of the ’794 patent	
CINV	Chemotherapy-induced nausea and vomiting	
CN ’845	Chinese Patent Appl. Pub. No. 102379845 (A)	JTX-71
Emend IV	Emend for Injection	
EP ’279	Bombardelli et al., EP0441279A1 (published Aug. 14, 1991)	JTX-74
FDA	United States Food and Drug Administration	
Fell	Fell et al., *Intravenous Lipid Emulsions in Parenteral Nutrition*, 6 Advanced Nutrition 600 (2015),	JTX-76
Fresenius	Defendant Fresenius Kabi USA, LLC	
Fresenius’s ANDA	ANDA No. 214639	
Fresenius’s ANDA Product	The drug product that is the subject of ANDA No. 214639	
Hargreaves	Richard Hargreaves et al., *Development of Aprepitant, the First Neurokinin-1 Receptor Antagonist for the Prevention of Chemotherapy-Induced Nausea and Vomiting*, 1222 Annals N.Y. Acad. Scis. 40 (2012)	JTX-82
HEC	Highly emetogenic chemotherapy	
Heron	Plaintiff Heron Therapeutics, Inc.	
Hingorani	U.S. Patent Appl. Pub. No. 2013/0317016 A1	JTX-105
ISAE	Infusion site adverse events	
IV	Intravenous	
Jumaa	Jumaa et al., *Lipid Emulsions as a Novel System to Reduce the Hemolytic Activity of Lytic Agents*, Eur. J. Pharm. Sci. 2000 (285-290)	JTX-88
Kamat	Kamat and DeLuca, “Chapter 5: Formulation Development of Small and Large Volume Injections,” in *Pharmaceutical Dosage Forms: Parenteral Medications, Third Edition*, 2010	JTX-92
Karavas	International Patent Appl. Pub. No. WO 2014/005606 A1	JTX-90
Khan	Khan et al., *Basics of Pharmaceutical Emulsions: A Review*, 25 African J. Pharmacy & Pharmacology 2715 (2011)	JTX-91

Table of Abbreviations (continued)

ABBREVIATION	MEANING	EXHIBIT NO.
Leal 2014	Leal et al., *Fosaprepitant-Induced Phlebitis: A Focus on Patients Receiving Doxorubicin/Cyclophosphamide Therapy*, 22 Support Care Cancer 1313 (2014)	JTX-137
Liu	Liu et al., *Progress in Research of Injectable Microemulsion*, 42 Chin. J. Pharm. 300 (2011) - Legaltranslation.biz	JTX-93
MEC	Moderately emetogenic chemotherapy	
NCCN	National Comprehensive Cancer Network	
NK-1	Neurokinin-1	
Patents-in-suit	U.S. Patent Nos. 9,561,229 and 9,974,794	
PFAT5	Population of large-diameter fat globules greater than 5 µm	
POSA	Person of ordinary skill in the art	
Rabinow	Rabinow, *Nanosuspensions in Drug Delivery*, SEPTEMBER 2004 | VOLUME 3, www.nature.com/reviews/drugdisc	JTX-183
RLD	Reference Listed Drug	
Strickley	Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, **2004,** *21*, 201-230	JTX-105
USP	United States Pharmacopeia	
Von Corswant	Von Corswant et al., U.S. Application No. 2001/0007663 (published July 12, 2001)	JTX-110
Wan	U.S. Patent Appl. Pub. No. 2011/0038925 A1	JTX-112
Washington	Washington, *Stability of Lipid Emulsions for Drug Delivery*, 20 Advanced Drug Delivery Revs. 131 (1996)	JTX-113
Yue	Yue et al., Process Optimization, Characterization and Evaluation In Vivo of Oxymatrine-Phospholipid Complex, 387 Int'l J. Pharmaceutics 139 (2010)	JTX-114
Zhou	Zhou et al., "Preparation of Aprepitant Emulsion for Intravenous Injection," *Chinese Journal of Pharmaceuticals*, **2012,** *43*, 1003-1006	JTX-115

I. INTRODUCTION

The inventors of the patents-in-suit, Drs. Thomas Ottoboni and Hannah Han, accomplished what others in the field could not: an intravenous aprepitant formulation for treating patients with CINV. Embodied in Heron's Cinvanti® product, this invention satisfied a long-felt but unmet need for a safe and effective intravenous NK-1 receptor antagonist with minimal side effects. As Heron's expert Dr. Jeffrey Hale, an inventor of the aprepitant molecule, explained, although aprepitant had been known for more than 20 years, its challenging physical properties—such as extremely low solubility (akin to "cement dust")—were thought to preclude formulation as an intravenous drug product. Indeed, Merck, the company that invented aprepitant, was unable to create an intravenous aprepitant product, and instead was forced to develop the prodrug fosaprepitant. While fosaprepitant was able to take a different path around the difficult physical attributes of aprepitant, it was formulated with polysorbate 80, an ingredient which causes adverse injection site reactions. In contrast, Heron succeeded in developing a stable intravenous aprepitant emulsion by using an unprecedented amount (14%) of the emulsifier egg lecithin in combination with other specific ingredients at specific concentrations and conditions. To date, Heron's Cinvanti® product remains the only FDA-approved intravenous formulation of aprepitant.

Fresenius's ANDA Product infringes claims 9, 10, and 21 of the '229 patent. *See* D.I. 150 at 18; D.I. 174 at 3. The sole remaining infringement issue for trial for claims 9 and 10 of the '794 patent was whether Fresenius's ANDA Product is "physically stable" under the Court's construction of that term. *Id.* Heron's formulation expert, Dr. Steven Little, showed that Fresenius's ANDA Product meets the three physical stability requirements, including that no aprepitant crystals are present in Fresenius's ANDA Product after at least seven days under 4x to 10x optical microscopy, which provides a total magnification of 40x to 100x. Indeed, Fresenius performed an even more stringent test for its product, which plainly shows that it lacks any such

crystals, and Fresenius's ANDA Product has the same formulation as Cinvanti®, which indisputably meets this criterion. Moreover, Fresenius's formulation expert, Dr. Barrett Rabinow, admitted that he has no reason to believe Fresenius's ANDA Product is not "physically stable," and that it does not contain aprepitant crystals when viewed under a magnification of 40x to 100x. Heron met, and exceeded, its burden of proving infringement by a preponderance of the evidence.

With no credible noninfringement defense, Fresenius asserts obviousness, contending that a POSA would have engaged in routine optimization and obviously arrived at the claimed aprepitant emulsion formulations. But that defense, as well as Dr. Rabinow's underlying testimony, rested on impermissible hindsight, and failed to satisfy the demanding standard of proving invalidity by clear and convincing evidence. Dr. Rabinow's analysis started with the claimed invention and worked backwards, rather than viewing the prior art through the lens of a POSA at the priority date. Indeed, Dr. Rabinow admitted that the starting point of his analysis was a POSA who was ***already*** focused on developing an intravenous aprepitant emulsion. This ignores both that there were NK-1 receptor antagonists other than aprepitant and formulation techniques other than an emulsions that a POSA would have considered when looking to develop an intravenous NK-1 receptor antagonist with minimal side effects.

According to Dr. Rabinow, a POSA would have immediately zeroed in on CN '845 (JTX-71) (which was expressly overcome during prosecution), a patent application that never issued as a patent, never became a product, contained no experimental data, and discussed broad ranges of multiple different ingredients. But he did not then assert that a POSA would seek to optimize an actual formulation within the broad disclosures and concentration ranges for ingredients in CN '845, *e.g.*, the emulsifier concentration in CN '845 is 0.5% to 10%. Dr. Rabinow manufactured a theory, tainted by hindsight, of why a POSA would have increased

the emulsifier concentration to 14% as in Asserted Claims, and also selected the other claimed ingredients, concentrations, and conditions.

The premise of Fresenius's argument is that CN '845 was a "game changer" when it came to emulsion formulation, even though it never issued as a patent and was not embodied by any actual drug products. But there was no evidence of CN '845 being a "game changer," and neither CN '845 nor the prior art that Dr. Rabinow asserts would have motivated a POSA to arrive at Heron's inventive combination. The very research group that published CN '845 continued its work with aprepitant emulsions and published Zhou (JTX-115). They did what Dr. Rabinow said a POSA would do, which was to "optimize" their previous work. And their result was an aprepitant emulsion that contained 2.5% egg lecithin, within CN '845's broad disclosure of 0.5% to 10% emulsifier. This "optimal" formulation used *less* egg lecithin than the upper limit of 10%. It did not *exceed* the upper limit. And that optimal amount bore a striking resemblance to the industry standard for emulsifiers like egg lecithin at the time of about 1.2%. So, even accepting that CN '845 was of momentary interest for disclosing up to 10% emulsifier, a POSA would have seen that the same researchers subsequently honed this new feature to just 2.5% egg lecithin. A POSA would not take the "game changer" and then ignore it, as Dr. Rabinow posited. Indeed, the Federal Circuit has rejected—on summary judgment—hindsight arguments about picking prior art for a supposedly important teaching and then just ignoring that teaching. Nothing pointed in the direction of 14% egg lecithin, let alone to the specific combination with other ingredients, like sodium oleate, which was not disclosed in CN '845 or Zhou.

Even after ignoring Zhou and industry standards, Dr. Rabinow's analysis did not touch the claimed emulsion—he still needed to reach outside of the relevant art and cobble together disparate references. For example, Dr. Rabinow asserted that a POSA would have interpreted CN '845 as

disclosing "complexation" of aprepitant and emulsifier and thereby providing a motivation to experiment with even higher concentrations of egg lecithin. But CN '845 did not even mention the word complexation, let alone show that complexation occurred. The complexation-related references that Dr. Rabinow relied on did not relate to intravenous products and, in fact, used a ratio of emulsifier to drug of just 3:1—not 20:1 like the Asserted Claims. With no other options, Dr. Rabinow then reached even farther afield to a mention of a percentage in a reference (Liu) in the thermodynamically distinct art of microemulsions, not even discussing egg lecithin, to try to find higher surfactant content. This is the epitome of hindsight. Moreover, with such scattershot mixing-and-matching approach, a POSA would not have had a reasonable expectation of success, because, for example, no prior art emulsion ever had the claimed combination of ingredients, or anything close to the high amount of emulsifier of 14% lecithin.

Objective indicia further confirm the nonobviousness of the patents-in-suit. Dr. Hale and Heron's clinical expert, Dr. Eric Roeland, demonstrated that there had been a long-felt but unmet need for an intravenous NK-1 receptor antagonist with minimal side effects, even after the launch of Merck's intravenous fosaprepitant product with polysorbate 80, Emend® IV. Cinvanti®, in contrast, lacks this problematic excipient and has reduced side effects. Dr. Hale also explained that Merck developed Emend® IV only after it tried and failed to develop intravenous aprepitant. Dr. Little further explained that Heron's claimed invention demonstrated unexpected results, including unexpected stability. And Heron's economic expert, Michael Tate, explained that Cinvanti® has been a commercial success.

Fresenius also made two cursory attempts at trial to assert invalidity for lack of written description. Each failed to come anywhere close to the heavy burden of clear and convincing evidence. Dr. Rabinow argued that the claimed pH range of 7.5 to 9.0 lacks support just because

the patents' examples used a range of 8.7 to 8.8. But that, of course, is not the legal test for written description (if a claim had to be a picture of an example to be valid, then virtually every patent would be invalid). The evidence showed that the inventors possessed the claimed range based on the specification's coextensive disclosures (*e.g.*, "7.5 to 9"). Fresenius's clinical expert, Dr. Maurie Markman, separately argued in the alternative to Fresenius's obviousness argument that the patents-in-suit lack support for use of aprepitant to treat CINV, because they do not contain clinical data. But, even Fresenius's experts concede that use of aprepitant to treat CINV was well known at the time of the invention, and the patents include positive *in vivo* pharmacokinetic data.

II. BACKGROUND

A. CINV and NK-1 Receptor Antagonists

CINV is a major concern for patients undergoing chemotherapy. CINV can greatly impact the quality of life of patients with cancer, and in some cases can be so severe that patients are unwilling to continue chemotherapy treatment. *See* TD2 569:6-570:11 (Markman); TD3 1010:821 (Roeland); JTX-128.6. The optimal treatment for CINV is preventing it, which involves using antiemetic medications to block certain neurotransmitters associated with nausea and vomiting. *See* TD3 1010:22-1011:16, 1014:8-1015:14 (Roeland). One such class of antiemetics is known as NK-1 receptor antagonists.

Aprepitant, the active ingredient in Cinvanti®, was the first NK-1 receptor antagonist used to treat CINV. *See* JTX-142.14; TD3 892:13-14, 894:2-8 (Hale); TD3 1013:6-25, 1014:8-1016:10 (Roeland). In 2003, oral aprepitant was first approved by the FDA under the brand name Emend®. JTX-82.4-5; TD3 913:4-13 (Hale). However, there remained a need for an intravenous NK-1 receptor antagonist because it provided better bioavailability and patient adherence compared to oral antiemetics. *See* TD3 1017:12-1018:23, 1020:8-1021:7 (Roeland). Merck had already faced challenges developing even an oral formulation of aprepitant (TD3 909:6-913:3 (Hale)), and, when

it came to an intravenous formulation, was forced to abandon its efforts after many failed attempts, viewing the drug's properties as precluding development altogether (TD3 917:23-919:1 (Hale) ("[T]hey essentially hit a brick wall."); JTX-82.5 ("The sparing water solubility of aprepitant precluded its formulation in a vehicle acceptable for intravenous administration in humans.")). Merck instead developed a prodrug of aprepitant, fosaprepitant, formulated with polysorbate 80 and approved by the FDA in 2008 as Emend® IV. TD3 937:12-938:1, 942:7-22 (Hale).

As of the priority date, September 19, 2014, the FDA-approved NK-1 receptor antagonists were oral aprepitant, marketed by Merck as Emend®, and an intravenous fosaprepitant product, marketed by Merck as Emend® IV. TD3 913:4-13, 942:7-22 (Hale). Several other NK-1 receptor antagonists were also being studied or under development at the time. Two had also succeeded in Phase III studies—netupitant and rolapitant. TD3 944:17-945:11 (Hale); TD4 1272:3-9 (Little).

B. Invention Behind the Patents-in-Suit

Dr. Tom Ottoboni, one of the inventors of the patents-in-suit, led Heron's research into NK-1 receptor antagonists. TD2 517:17-521:1 (Ottoboni). By then, Dr. Ottoboni already had significant experience with drug formulations, among other things, and was an inventor on patents covering a variety of technologies, including in the field of drug delivery, microparticles, emulsions, and polyorthoester-based delivery stems. TD2 515:25-517:3 (Ottoboni); JTX-2.125.

Heron's work included research into parenteral formulations of fosaprepitant. TD2 518:16-519:22 (Ottoboni). For example, Dr. Ottoboni described an extended-release formulation of Emend® IV that was administered subcutaneously to dogs. *Id*. This experiment resulted in "a very profound adverse event," with the dogs suffering an anaphylactic reaction within minutes of administration. TD2 519:5-520:2 (Ottoboni). Heron's parenteral NK-1 receptor antagonist research also included a number of intravenous formulation approaches, the major ones involving cosolvents and surfactants. TD2 520:7-17 (Ottoboni). Eventually, Dr. Ottoboni suggested

aprepitant emulsions as a potential solution. TD2 520:22-521:1 (Ottoboni).

Dr. Ottoboni supervised and worked closely with Dr. Hannah Han, the other inventor of the patents-in-suit. *E.g.*, TD2 467:4-7, 506:5-12, 508:1-16 (Han); TD2 523:13-16, 540:13-24 (Ottoboni). Dr. Han's responsibilities included preparing and conducting many experiments. TD2 464:19-465:6, 473:22-474:14, 475:7-21, 477:8-15 (Han); TD2 541:9-22 (Ottoboni). Heron's experiments on parenteral NK-1 receptor antagonists were detailed in hundreds of pages of laboratory notebooks. *E.g.*, DTX-191, DTX-193, DTX-259.

As part of their experimentation, Drs. Ottoboni and Han tried many different approaches with emulsions, including a variety of ingredients. *E.g.*, DTX-259.254, .278-79; *see also* TD2 465:1-6, 477:8-15 (Han); TD2 542:15-543:2 (Ottoboni). In a departure from all prior conventions, Heron's intravenous NK-1 receptor antagonist program experimented with an amount of emulsifier that went far beyond anything in the prior art. *See infra* § IV.E.1. Many experiments resulted in crystals and/or phase separations (creaming, flocculation), among other failures. *See, e.g.*, DTX-259.190-200, .247-51, .254-63, .289-91. And, the inventors explained that numerous experiments were necessary to obtain a stable product. TD2 465:1-6, 477:8-478:3, 508:1-16 (Han); TD2 541:9-542:7, 542:15-543:2 (Ottoboni).

As Dr. Han explained, "[t]he emulsion is very complex. The ratio of lecithin to aprepitant, oil to aprepitant, sodium oleate used, everything is important to make a stable emulsion. And Tom and I – Tom and I came up with this together through a lot of trial-and-error experiments."[1] TD2 508:1-16 (Han). Eventually, Drs. Ottoboni and Han's research resulted in the first and still only intravenous aprepitant product that could be given to patients. TD2 506:5-12 (Han); TD3

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[1] The amount of lecithin, in combination with other ingredients, was ultimately critical for the developing a stable product. *See* TD2 509:18-510:7 (Han); JTX-2.162. Aprepitant, however, is not soluble in lecithin on its own. TD2 474:1-14 (Han).

1040:15-23 (Roeland); TD4 1343:13-1344:6, 1348:2-13 (Little). The commercialized formulation, now known as Cinvanti®, is used to directly administer aprepitant and help cancer patients undergo chemotherapy with minimal side effects compared to the prior intravenous NK-1 receptor antagonist, Emend® IV. TD3 1058:17-1059:2, 1060:9-1061:2 (Roeland).

C. The Patents-in-Suit

The patents-in-suit are titled "Emulsion Formulations of Aprepitant" and describe novel pharmaceutical emulsion formulations of aprepitant suitable for intravenous administration for the treatment of emesis.[2] The relevant invention date for purposes of this case is the priority date of September 19, 2014. JTX-1; JTX-7. Heron asserts that Fresenius's ANDA Product infringes claims 9, 10, and 21 of the '229 patent and claims 9 and 10 of the '794 patent.

1. The Patent Examples of Physically Stable Emulsions

The patents-in-suit provide exemplary formulations and data from research Heron conducted, including eleven examples. Examples 1-3 and 6 disclose aprepitant emulsion formulations. *See* JTX-1.14-16 (16:37-50 (Ex. 1), 17:20-33 (Ex. 2), 18:1-14 (Ex. 3), 20:14-30 (Ex. 6)). Example 7 provides stability testing of the formulations prepared in Examples 1-3 and 6, including mean droplet size and PFAT5 under USP <729>,[3] and evaluating for aprepitant crystals. *See* JTX-1.16-17 (20:31-21:10). The inventors found that the formulations of Examples 1, 3, and 6 were stable at 25° C for 2 months, while the formulation of Example 2 was stable under the same conditions for 3 months. *Id.* Each of Examples 1-3 and 6 were also stable at 5° C for more than 10 months. *Id.*

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[2] The specifications of the patents-in-suit are substantially the same, therefore citations are made to the '229 patent for ease of reference. *Compare* JTX-1 *with* JTX-7.

[3] USP<729> refers to Chapter 729 of the USP. PFAT5 refers to the population of large-diameter fat globules greater than 5 µm. *See* TD1 17:7-17 (Little).

Examples 9 and 10 of the patents-in-suit describe pharmacokinetic studies where the formulations described in Examples 1 and 6, along with aprepitant's prodrug fosaprepitant, were intravenously administered to rats. *See* JTX-1.17; TD2 698:17-699:22 (Markman). These examples provide the plasma concentration of aprepitant in rats following administration of these formulations. This data shows the favorable bioavailability of aprepitant in those formulations.

2. The Patent Examples of Prior Art Emulsions

Examples 4 and 5 are identified as "Alternate Aprepitant Emulsion Formulation for Intravenous Injection." *See* JTX-1.15-16 (18:16-17). These examples discuss formulations using ingredients and concentrations of those ingredients that were disclosed in the prior art, including CN '845 and Zhou. *See* TD4 1326:2-1327:25, 1402:2-5 (Little). As discussed in Section IV.E.1, CN '845 disclosed ranges of ingredients and with no stability testing or data, and Zhou tested a specific formulation but did not test for aprepitant crystallization or PFAT5. These examples, which are outside the scope of the claims of the patents-in-suit, were not physically stable.

The Example 4 formulation has ingredients and concentrations that were disclosed in CN '845, and was adjusted to pH 7.0. JTX-1.15 at 18:20-58; *see also* TD2 499:4-21 (Han). Dr. Han testified that she used her best efforts to choose a formulation based on CN '845 that she thought would have the best chance at success. *See* TD2 490:21-491:5, 492:23-493:16 (Han); TD2 541:9-542:1 (Ottoboni). Indeed, 9.95% egg yolk lecithin was used, which goes right up to the 10% limit disclosed in CN '845. The formulation was not stable and within four days post preparation at room temperature, crystals were observed in the product by microscopy. *See* JTX-1.15 (18:44-46); TD2 490:25-491:10 (Han); TD2 542:8-14 (Ottoboni); TD2 406:4-9 (Rabinow); TD4 1246:15-1247:9 (Little).

The Example 5 formulation has the ingredients and concentrations of the Zhou formulation, which the parties' experts agreed was accurately reproduced. *Compare* JTX-1.15-16 (18:60-

19:26) *with* JTX-115.1; *see also* TD2 545:16-546:21, 547:14-22 (Ottoboni); TD2 409:21-410:19, 411:7-10 (Rabinow); TD4 1269:4-15, 1345:8-11, 1402:2-5 (Little). Zhou was an "optimized" formulation of CN '845. TD1 323:20-324:7, 328:24-329:4, 349:2-7 (Rabinow); TD4 1257:10-14 (Little); JTX-115.1. This formulation was not stable and within four days post-preparation at room temperature, crystals were observed in the product by microscopy. *See* JTX-1.16 (19:12-14); TD2 409:7-11 (Rabinow); TD4 1269:12-1270:1 (Little).

Dr. Rabinow's testimony raised two arguments regarding Example 4 in the patents-in-suit: (1) that Example 4 "did not replicate any specific formulation that was done in [CN '845]" (TD1 289:10-15 (Rabinow)) and (2) that the inventors selected the wrong pH value because "Heron's formulations were all formulated at a pH of around 8.7 to 8.8, whereas the CN formulations were formulated around pH 7" (TD1 286:6-17 (Rabinow)). Turning to the first argument, the patent did not portray Example 4 as one of the specific formulations in CN '845. Rather, as noted above, Example 4 provided a formulation within the disclosed ranges of CN '845, including with respect to pH. *See* TD4 1327:6-25 (Little); *see also* TD2 406:10-23 (Rabinow). Further, the inventors stated that they applied the lessons learned from their internal research to make a formulation using ingredients and concentrations disclosed in CN '845. TD2 490:21-491:5, 492:1-493:16 (Han); TD2 541:9-542:1 (Ottoboni). These choices were made as part of their research, filed with the patent specification—not created in response to patent prosecution.

Heron later explained to the Patent Office that Examples 4 and 5 formed crystals within four days and that this showed the poor stability of the emulsions disclosed in CN '845 (which itself disclosed no stability data). Dr. Ottoboni explained that the examiner had some questions regarding the method of preparation of Example 4 of the patents-in-suit and Example 1 of CN '845

to which he responded.[4] TD2 534:13-535:11 (Ottoboni). In addition, Dr. Ottoboni explained to the examiner that "the instant claims were not obvious over [CN '845] for at least the reason that the claimed pharmaceutical emulsion possessed unexpected and unpredictable properties relative to [CN '845]." JTX-2.126.

With respect to the second argument, according to Dr. Rabinow, the inventors should have used a pH greater than 8 in order to control for all variables other than the amount of egg lecithin. TD1 286:6-290:18 (Rabinow). But the experiment was not some research experiment to explore pH. The testing was looking at the performance of a formulation in accordance with the prior art, and comparing that formulation to the invention. CN '845 disclosed a pH range of 6-8. TD2 406:10-12 (Rabinow). The pH of Example 4 was 7.0, squarely in the middle of the pH range that CN '845 disclosed. TD2 406:13-23 (Rabinow). Moreover, Fresenius's own ANDA Product permits a pH range of 7.0 to 8.6. TD1 24:21-25:4 (Little); JTX-33.1.

Fresenius, a company that makes emulsions and had the facilities to test emulsions, and Dr. Rabinow—an expert that could have overseen a lab to conduct emulsion testing—could have but did not present any testing of the formulations of Examples 4 and 5 or any other formulation of CN '845 or Zhou for that matter. *See* TD2 411:11-22 (Rabinow).

D. The File History of the Patents-in-Suit

Fresenius did not rely on a single document disclosing a formulation of aprepitant for intravenous use that the examiner had not already considered in allowing the claims. The combination of prior art that Dr. Rabinow presented at trial as the basis of obviousness was CN

[4] Dr. Rabinow asserted that the examiner was "asking for . . . [a] side-by-side comparison of the formulation done by Heron compared to those of [CN '845]," (TD2 288:19-289:15 (Rabinow)), but this is incorrect. Examples 4 and 5 were already in the as-filed specification that was submitted for review by the examiner. *See, e.g.*, JTX-2.33-34; TD2 530:10-20 (Ottoboni).

’845, Zhou, and the knowledge of a POSA. TD1 305:11-23 (Rabinow). Regarding CN ’845, the examiner concluded that “[t]he wt. % of the egg yolk lecithin is far too low, as is the ratio of egg yolk lecithin to aprepitant.” *See* JTX-2.163. And, regarding Zhou, the examiner concluded that it “provide[d] insufficient motivation to increase the amount of egg yolk lecithin in the composition, or to provide a higher ratio of egg yolk lecithin / emulsifier to aprepitant.” *See* JTX-8.159. Because these references were already considered by the examiner, Fresenius and its experts bear a particularly heavy burden to prove invalidity. *See Metabolite Lab’ys., Inc. v. Lab’y. Corp. of Am. Holdings*, 370 F.3d 1354, 1368 (Fed. Cir. 2004); *Impax Lab’ys., Inc. v. Aventis Pharm. Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008) (“When the examiner considered the asserted prior art and basis for the validity challenge during patent prosecution, that burden becomes particularly heavy.”).[5]

In allowing the claims, the examiner expressly stated that she looked for, but could not find, any emulsions with an NK-1 receptor antagonist with the claimed amount of emulsifier. *See* JTX-2.162. The examiner also stated that Heron “demonstrated criticality of the range in regard to the wt. / wt. % egg yolk lecithin and the ratio of egg yolk lecithin to aprepitant” and that this could be viewed as either a demonstration of criticality or unexpected results. *See id.*

E. Cinvanti®

Heron holds NDA No. 209296 for an injectable emulsion for intravenous use containing 130mg/18mL (7.2 mg/mL) aprepitant as the active ingredient, which it markets and sells in the United States as Cinvanti®. Cinvanti® was approved by the FDA on November 9, 2017 and launched in the first quarter of 2018. For this NDA, Heron demonstrated that Cinvanti® is physically stable. *See* JTX-49.4-6, .41-43, .47-49; *see also* TD1 15:5-23:22 (Little). Cinvanti® is

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[5] Unless stated otherwise, all internal quotations and citations are omitted, and all emphases added.

indicated in adults, in combination with other antiemetic agents, for treating emesis. *See* JTX-51.1-2. Pursuant to 21 U.S.C. § 355(b)(1), Heron listed, *inter alia*, the '229 patent and the '794 patent in the Orange Book as covering the FDA-approved uses of Cinvanti®.

III. Fresenius's ANDA Product Infringes All of the Asserted Claims

Before trial, this Court determined Fresenius's ANDA Product infringes claims 9 and 10 of the '229 patent. D.I. 150 at 18. Fresenius also conceded that its ANDA Product infringes claim 21 of the '229 patent. D.I. 174 at 3. The sole remaining infringement dispute for trial was whether Fresenius's ANDA Product meets the "physically stable"[6] claim limitation of claims 9 and 10 of the '794 patent.[7] *Id.*

A. Fresenius's ANDA Product

Fresenius filed ANDA No. 214639 with the FDA seeking approval for Aprepitant Injectable Emulsion, 130 mg/ 18 mL (7.2 mg/mL) in 20 mL single-dose vials. The RLD for Fresenius's ANDA Product is Cinvanti®. The batch formula for Fresenius's ANDA Product is set out in ANDA No. 214639. JTX-37.1.

In its FDA submission, Fresenius explained that the formulation of its ANDA Product is the same as the Cinvanti®. *See, e.g.*, JTX-189.23 ("formulation is the same as . . . Cinvanti®"), JTX-190.3, JTX-192.2; *see also* TD1 24:1-16, 24:21-25:4, 27:24-28:19, 29:4-13 (Little); TD1

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[6] The Court construed "physically stable" to mean "[m]eets the criteria under USP<729> for mean droplet size not exceeding 500 nm and PFAT5 not exceeding 0.05%, and no visible aprepitant crystals when viewed at magnification of 4x to 10x, after being stored either at 5º Celsius or at room temperature for a period of at least one week." D.I. 54 at 14-15.

[7] There can be no dispute as to any other limitations because the remaining limitations are the same as claims 9 and 10 in the '229 patent that have been found to infringe. D.I 150; *see also* JTX-189.23 ("FK USA's drug product formulation is the same as that of Cinvanti®"); JTX-192.2 ("the proposed drug product is identical to [Cinvanti®]"); TD1 27:24-28:19 (identical wt/wt % amounts), 29:4-13 (formulation meets all the claim elements), 24:21-25:4 (Fresenius ANDA acceptance criteria pH needs to be between 7.0 and 8.6) 42:21-43:12 (pH of exhibit batches) (Little); JTX-33.1 (pH acceptance range).

85:5-19, 88:1-6, 89:8-19 (Schmitt); JTX-33.1. Similarly, Fresenius included the following table in its ANDA showing that its product's formulation is exactly the same as Cinvanti®'s:

Table 5.3.1.3- 2 Comparison of FK USA's and RLD Formulation (Cinvanti®)

Ingredients	Cinvanti®	Aprepitant Injectable Emulsion	
	Heron Therapeutics	FK USA	
	Per Container	Per mL	Per Container
Aprepitant	130 mg	7.2 mg	130 mg
Egg Lecithin	2.6 g	144.4 mg	2.6 g
Ethanol	0.5 g	28.5 mg	0.5 g
Sodium Oleate	0.1 g	4.8 mg	0.1 g
Soybean Oil	1.7 g	96.0 mg	1.7 g
Sucrose	1 g	54.0 mg	1 g
Water for Injection	12 g	666.7mg	12 g

JTX-43.5. Fresenius likewise told the FDA that "[t]he physicochemical properties of the proposed drug product, Aprepitant Injectable Emulsion, are equivalent to those of Cinvanti®, the RLD as the proposed product is demonstrated Q1/Q2/Q3 equivalent to the RLD." JTX-26.75.

B. Fresenius's ANDA Product Infringes Claims 9 and 10 of the '794 Patent

There is no dispute that Fresenius's ANDA Product satisfies the first two criteria for "physical stability" under the Court's construction. That is, Fresenius's ANDA Product is listed as having (1) a mean droplet size of 45 to 75 nm, which does not exceed 500 nm and (2) a PFAT5 of not more than 0.05%, through 12 months of storage at 5 °C ± 3 °C and through 6 months of storage at 25 °C ± 2 °C (room temperature). TD1 32:15-33:4 (mean droplet size of 45 to 75 nm and PFAT5 not more than 0.05%) (Little); TD1 101:17-103:16 (acceptance criteria is mean globule size of 45 to 75 nm and PFAT5 of not more than 0.05%), 105:17-106:18, 107:6-109:9, 110:21-111:17 (Xiao); JTX-33.2; JTX-35.2 (all stability criteria met by exhibit batches).

The evidence at trial demonstrated that Fresenius's ANDA Product also satisfies the third, and final, criterion for physical stability—"no visible aprepitant crystals when viewed at magnification of 4x to 10x, after being stored either at 5º Celsius or at room temperature for a

period of at least one week"—for at least three reasons.[8]

First, "[w]hat [Fresenius] has asked the FDA to approve as a regulatory matter" controls, and Fresenius is seeking approval for a product that does not contain aprepitant crystals under the stated conditions. *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1278-79 (Fed. Cir. 2013); *see also* TD1 33:11-36:20 (The goal of Fresenius's acceptance criteria is no crystals observed after ultracentrifugation and all of Fresenius's exhibit batches met this criteria) (Little); JTX-33.2 (Fresenius's ANDA Product acceptance criteria for crystal content is: "No crystals observed after ultracentrifugation[.] If crystals observed after ultracentrifugation, [not more than] 1.5%[.]"). Fresenius's expert, Dr. Rabinow, did not provide testimony to the contrary.

Second, Fresenius's ANDA reports that its ANDA Product has no crystals after ultracentrifugation. JTX-33.2 ("[n]o crystals observed after ultracentrifugation"); TD1 33:11-36:20 (no crystals observed after ultracentrifugation) (Little). The undisputed testimony at trial was that Fresenius's ultracentrifugation test is more stringent for detecting aprepitant crystals than the visibility test under 4x to 10x magnification. *See* TD1 36:22-37:12 (explaining that centrifugation is a "more [stringent] test than if you just took one drop of it and you looked at it under the [4x to 10x] magnification that we are talking about") (Little). And, Fresenius's exhibit batches contained no observable crystals using this ultracentrifugation test "through the 6-month test station for accelerated (25°C ± 2°C/60% ± 5% RH) and 12-month long-term (5°C ± 3°C) storage." *See* JTX-34.14 ("no crystals observed after ultracentrifugation"); JTX-35.2 (all stability criteria met for Fresenius's exhibit batches); JTX-28.4-.12, .27 (ultracentrifuge testing procedure);

[8] As Dr. Little explained, the specification of the patents-in-suit is clear that "magnification of 4x to 10x" refers to selection of the objective lens, and, when combined with the standard 10x eyepiece lens, provides a total magnification of 40x to 100x. TD1 22:9-24, 23:4-12, 69:13-23, 70:4-73:20 (Little); JTX-1.3 (FIGs 1A-1D). Dr. Rabinow did not dispute this basic scientific fact.

TD1 35:3-11, 36:15-20 (no crystals through 6 months at 25°C and 12 months at 5°C) (Little); TD1 103:17-104:20 (No crystal content has been observed in any of Fresenius's exhibit batches through 6 months at 25 °C ± 2 °C and 12 months at 5 °C ± 3 °C) (Xiao). Any argument that Fresenius did not test its ANDA Product using the exact test identified for the term "physically stable" is irrelevant. *See Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, 477 F.Supp.3d 306, 343 (D. Del. 2020) ("[T]here is no requirement [to prove infringement] in the precise manner an accused infringer demands.").

Finally, Cinvanti®, which is an embodiment of the Asserted Claims (TD1 19:23-20:20 (Little); JTX-1.18, JTX-45.1, JTX-47.1-2), has "no visible aprepitant crystals when viewed at magnification of 4x to 10x." TD1 21:2-22:21 (Little); JTX-49.4, .41-.43, .47-.49 (Tables 3.2.P.8.3-14 and 3.2.P.8.3-16, showing no crystals after 6 months at 25°C and after 12 months at 2-8°C in Cinvanti®). And, Fresenius has represented to the FDA that its ANDA Product is "identical to" Cinvanti® (JTX-192.2) and that there were no "evidence or differences in stability or other characteristics between Fresenius Kabi USA's drug product and [Cinvanti®] that would present concerns with therapeutic equivalence." TD1 27:2-15 (discussing that JTX-26.10 affirms Q1/Q2 equivalence) (Little); *see also* TD1 37:16-38:24 (Little); TD1 87:6-20 ("We believe it's Q1/Q2.") (Schmitt); TD1 99:7-11 (affirming Q1/Q2 equivalence) (Xiao). Therefore, Fresenius's ANDA Product meets the same physical stability criteria that Cinvanti® does, including that it has "no visible aprepitant crystals when viewed at magnification of 4x to 10x."

IV. Fresenius Failed to Prove Obviousness

Fresenius did not meet its high burden to show obviousness by clear and convincing evidence. The flaws in Dr. Rabinow's only obviousness ground—the combination of CN '845, Zhou, and the purported knowledge of a POSA (TD1 278:11-279:10 (Rabinow))—are manifold and, taken together, demonstrate that his analysis was tainted by improper hindsight.

A. Legal Standard

Obviousness under 35 U.S.C. § 103 requires proof by clear and convincing evidence. *See Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 97 (2011). Obviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill; and (4) objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Fresenius must prove by clear and convincing evidence that a POSA, at the time of the invention and without the benefit of hindsight, "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859-61 (Fed. Cir. 2015); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012).

B. The Priority Date and Dr. Rabinow's Hindsight-Driven Definition of a POSA Definition

Dr. Little and Dr. Rabinow provided the following descriptions of a POSA:

Dr. Little's Definition	Dr. Rabinow's Definition
A POSA at the time of the invention would have a bachelor's degree in chemistry, pharmaceutics, chemical engineering, or a related field, as well as three to five years of experience in formulating drug products, including parenteral drug products. This person could have an advanced degree in these fields and fewer years of experience. A POSA may also consult with individuals with experience in other disciplines. Such consultation would not alter the "ordinary" skill of the POSA who is receiving and using the information.	An individual with an advanced degree in pharmaceutical formulation, pharmaceutical chemistry, medicinal chemistry or a related field and experience with intravenous emulsion formulations. Such a person would also consult with or have access to a medical doctor specializing in oncology or a general practitioner having 2-3 years of experience treating patients with cancer.

See PDX4-2. Dr. Rabinow's definition uses improper hindsight to focus *a priori* on intravenous

emulsion formulations, whereas Dr. Little's definition relates to parenteral formulations generally. *See* TD4 1212:16-1214:3 (Little); *Insite*, 783 F.3d at 859-61 ("Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness."). Regardless, Fresenius failed to prove that any of the Asserted Claims would have been obvious using either Dr. Little's or Dr. Rabinow's definition of a POSA. *See* TD4 1214:6-14 (Little) (opinion would not change under either definition).

C. A POSA's Analysis Would Not Have Started with the Hindsight-Based Problem that Dr. Rabinow Asserts

As of September 2014, the problem facing a POSA was to develop a new IV NK-1 receptor antagonist that could provide a safe and effective treatment that had minimal side effects. TD4 1272:14-22 (Little). Emend® IV had provided an advancement in CINV treatment, but it "had some issues with tolerability" because of the "addition of an ingredient, polysorbate 80." TD4 1273:1-7 (Little); TD3 1035:6-12 (Roeland); *see also infra* § IV.H.1. These issues included significant infusion site adverse events and resulted in a warning being added to the Emend® IV label and the Mayo clinic reverting to oral Emend® over Emend® IV. *See infra* § IV.H.1.

Fresenius's obviousness position does not start with the problem that was facing a POSA. Instead, Fresenius relies on hindsight to narrowly focus on how "to make an injectable aprepitant formulation." TD1 278:11-23 (Rabinow). Indeed, Dr. Rabinow in his opening report improperly "focused on a POSA developing exclusively an IV ***aprepitant emulsion***." TD1 346:4-7 (Rabinow); *see Insite*, 783 F.3d at 859.

1. Fresenius Failed to Consider Other NK-1 Receptor Antagonists

As of the priority date, there were multiple NK-1 receptor antagonists that had succeeded in FDA phase III clinical trials for safety and efficacy in addition to aprepitant, including fosaprepitant, rolapitant, and netupitant. TD3 944:17-945:11 (Hale); TD4 1272:3-9 (Little). And

while Dr. Rabinow agreed "that POSAs were interested in NK-1 receptor antagonists as a class and not just aprepitant" (TD2 395:6-9, 279:11-280:2 (Rabinow)), he assumed that a POSA would have been looking exclusively at aprepitant when he originally provided his obviousness opinions. (TD1 346:4-7) (Rabinow)).

While aprepitant was known to be effective clinically, it was also known to have "challenging physical properties." TD3 901:17-902:5 (Hale); *see also* TD2 398:18-399:1 (Rabinow). Aprepitant molecules "really like to stick together." TD3 903:8-905:11 (Hale). These properties mean that aprepitant is "highly crystalline" and aprepitant molecules "readily [and] efficiently pile onto each other to form these crystals" like LEGO blocks. *Id.*; TD3 899:4-901:5 (Hale). As a result, aprepitant is largely insoluble. TD3 899:4-902:5 (Hale). And, even if aprepitant could be solubilized initially, experiments showed that it could "very quickly afterwards" form solid crystals. TD3 934:10-936:24 (Hale). In short, aprepitant both looked and behaved like "cement dust." TD3 899:4-901:5 (Hale).

Eventually, Merck concluded that the sparing solubility of aprepitant "precluded" its use in an intravenous formulation. JTX-82.0005; TD3 917:3-22 (Hale). Merck continued with the development of new NK-1 receptor antagonists that would maintain the good biologic properties of aprepitant but "also design and build in features of the molecule that would enhance solubility so that it would be more amenable to intravenous formulation." TD3 918:11-919:1 (Hale). The result of this research was the development of the prodrug fosaprepitant for its Emend® IV product. TD3 914:18-915:8, 937:4-938:1 (Hale); *see also* TD4 1270:7-1271:15 (Little).

Fosaprepitant has the same biologic properties of aprepitant but "is 6,000 times more soluble in isotonic saline than is aprepitant." TD3 938:15-21 (Hale); *see also* JTX-73.12 (fosaprepitant is "freely soluble in water"). Dr. Rabinow failed to explain why a POSA would

focus on aprepitant when fosaprepitant was available, and he even acknowledged that what a POSA would like to see next is "development of an injectable that did not contain the polysorbate 80"—specifically "[o]f the ***fosaprepitant*** IV formulation." TD1 125:17-24 (Rabinow). Even the prior art references relied upon by Dr. Rabinow describe formulations with NK-1 receptor antagonists other than aprepitant. For example, all of the examples in Karavas used fosaprepitant. *See* TD1 368:12-370:3 (Rabinow); JTX-90.12, .14, .17. And, all the formulations in Wan used rolapitant. TD2 426:1-3 (Rabinow); JTX-112.0001, .15, .27-40.

Dr. Rabinow selectively focused on the portions of his cited documents that mention aprepitant while ignoring the disclosures of other NK-1 antagonists. This is not consistent with the approach that a POSA would have taken. *See Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 921 (Fed. Cir. 2011) ("[I]t is impermissible to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.").[9]

2. Fresenius Failed to Consider Other Formulation Approaches

Dr. Rabinow admitted that a number of other formulation approaches would have been considered before emulsions when making an injectable product. TD1 271:13-24, 272:12-273:4, 278:11-279:10, 345:19-346:7 (Rabinow). Strickley provided a flow chart of suggested order of solubilization approaches for injectable formulations, and emulsions are second-from-the-bottom. JTX-105.26; *see also* TD1 272:12-273:4 (Rabinow); TD4 1274:14-1278:1 (Little). Kamat provides a similar approach. JTX-92.11-21, .31-42. Indeed, both references observed that intravenous emulsions were rarely used for a commercial product (JTX-105.25; JTX-92.33-34),

[9] Despite its interests in IV NK-1s and experience in emulsions, in 2014 Fresenius pursued IV fosaprepitant and did not pursue an aprepitant emulsion. TD2 404:32-405:22 (Rabinow).

and Strickley reported there was only one FDA-approved intravenous emulsion comprising an active ingredient at the time (TD1 1279:9-14 (Little); JTX-105.23). As Dr. Little explained, a POSA working with aprepitant "would begin to try to see if there are other formulation approaches that are simpler" and "work from simpler to more complex." TD4 1274:14-23 (Little). Dr. Rabinow similarly admitted that "if it is possible to formulate a drug using a simpler approach, by all means do so." TD1 266:12-19 (Rabinow).

Indeed, Dr. Rabinow published a 2004 review article recognizing that "you could use nanosuspensions if you're dealing with a compound that is insoluble in both water and oil." TD2 401:6-16 (Rabinow); JTX-183.1-2; *see also* TD1 274:22-275:16 (Rabinow). Yet, Dr. Rabinow did not consider the approach of formulating aprepitant as a nanosuspension despite describing aprepitant as "insoluble in both water and oil." TD1 121:3-10 (Rabinow). Additionally, Dr. Rabinow acknowledged that a combination of cosolvents and surfactants should be considered before emulsions (JTX-105.26; TD1 272:12-273:4 (Rabinow)), which was an approach taken in Hingorani (JTX-21.3-4, .7), but similarly ignored those in his obviousness analysis.

In sum, Dr. Rabinow started his obviousness analysis incorrectly presuming a POSA would have been working on an aprepitant emulsion, and ignored other formulation approaches a POSA would have considered. *See* TD1 346:4-7 (Rabinow); *see, e.g.*, *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) (A POSA is presumed to think "along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which.").

D. Dr. Rabinow's Hindsight-Driven 13-Reference Obviousness Combination

Dr. Rabinow alleged that the Asserted Claims were "obvious because the prior art clearly showed a formulation, such that the CN ['845] patent and Zhou, in combination with the knowledge of a person of ordinary skill in the art, would have been able to essentially reproduce

the patent." TD1 305:11-23 (Rabinow). Dr. Rabinow thus claimed that a POSA's goal would have been to "essentially ***reproduce*** the patent" (*id*.), but, in an obviousness analysis, a POSA would, of course, not have had the benefit of the patent. *See In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000) (noting the ease of "fall[ing] victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher").

Dr. Rabinow then attempted to incorporate no less than ***eleven*** different additional prior art references into a combination with CN '845 and Zhou at trial, including:

- JTX-82 (Hargreaves) (aprepitant background);
- JTX-90 (Karavas) (aprepitant emulsions);
- JTX-21 (Hingorani) (aprepitant emulsions);
- JTX-91 (Khan) (emulsifier in emulsions);
- JTX-93 (Liu) (microemulsions);
- JTX-113 (Washington) (structure of emulsions);
- JTX-114 (Yue) (phospholipid complex with oxymatrine);
- JTX-67 (Agarwal) (phospholipid complex with resveratrol);
- JTX-74 (EP '279) (phospholipid complex with bilobalide);
- JTX-88 (Jumaa) (sodium oleate); and
- JTX-112 (Wan) (sodium oleate).

As an initial matter, the sheer volume of disparate references needed to stitch together Dr. Rabinow's convoluted analysis only demonstrates the nonobviousness of the Asserted Claims. *See Endo Pharm Inc. v. Mylan Pharm. Inc.*, No. 11-CV-00717 (RMB/KW), 2014 WL 334178, at *14 (D. Del. Jan. 28, 2014) ("Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit."). But, more to the point, Fresenius's obviousness defense is legally deficient for presenting insufficient evidence of a POSA's motivation to actually combine all this disparate prior art in the specific and unprecedented way that Dr. Rabinow asserts. *See Cephalon Inc. v. Mylan Pharms. Inc.*, 962 F.Supp.2d 688, 714 (D. Del. 2013) ("[A] defendant asserting obviousness in view of a combination of references has

the burden to show that a person off ordinary skill in the relevant field had a reason to combine the elements in the manner claimed.”).

E. Fresenius Failed to Prove The Asserted Claims Were Obvious

1. Dr. Rabinow Used Hindsight to Focus on CN ’845 As a Basis for Further Research

Dr. Rabinow’s assertion that a POSA would have focused almost exclusively on CN ’845 for further research ignored the teachings of others, directly related prior art that post-dated it. Assuming, for the sake of argument, that a POSA did focus exclusively on developing an aprepitant emulsion, the POSA would have seen that CN ’845 disclosed using a broad range for emulsifiers from 0.5 to 10%. JTX-71.13; TD1 242:12-20, 314:18-20, 315:2-4, 331:2-6 (Rabinow); TD4 1220:18-1221:5, 1223:25-1224:3 (Little). CN ’845 likewise disclosed broad ranges for the amounts of other ingredients as well as a pH range spanning two full orders of magnitude (*i.e.*, pH 6.0 - 8.0). JTX-71.13; TD1 314:14-315:15, 331:7-13 (Rabinow); TD4 1217:10-1218:12 (Little). Dr. Rabinow’s demonstrative, DDX1-5, shows that his alleged obviousness analysis relied on the full ranges of multiple genuses of this disclosure:

CN’845 Ranges

	CN’845	Claims
Aprepitant	.05-2%	0.7%
Emulsifier	0.5-10%	14%
Oil	5-30%	9-10%
Sodium Oleate	pH adjuster	any amount
pH	6-8 pH	7.5-9 pH
Protective Agent	5-20%	5%
Co-Emulsifier	1-10%	2-6%

DDX1-5

DDX1-5; JTX-71.13; TD1 224:21-225:7, 227:18-228:14 (Rabinow); *see also* PDX4-4; TD4 1220:2-1223:24 (Little); *infra* § IV.E.2. CN ’845, however, did not contain ***any*** actual stability

data to support a conclusion that its disclosure produced stable emulsions, including for any of the three criteria for "physical stability." TD1 318:9-11 (Rabinow); *see also id*. at 189:7-14, 359:18-360:11 (Rabinow); TD4 1245:20-23 (Little).[10] In fact, that the only available data about CN '845, which is found in Example 4 of the patents-in-suit, shows its formulations were not stable. *See supra* § II.C.2; *see also* TD2 411:11-22 (Rabinow).

Dr. Rabinow similarly sidestepped all the CN '845 examples, which were described as "preferred embodiments." *See* TD1 349:14-350:6 (Rabinow); JTX-71.14. This only makes matters worse. *Eli Lilly v. Actavis*, 435 F. App'x at 921 ("[I]t is impermissible to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art."). As Dr. Little explained, and as shown below, there are "six claim elements spread throughout," and "there is no single example that meets the elements of the claim." TD4 1220:5-1222:15 (Little) (discussing PDX4-4) (highlighting shows outside claim limitation).

[10] Dr. Rabinow is wrong that a POSA would have interpreted terminal sterilization to mean the CN '845 examples were stable. TD1 318:12-319:3 (Rabinow). Dr. Little explained that terminal sterilization is simply a method of sterilizing (killing bacteria in) a product after it has been prepare, and is not a stability test. TD4 1226:15-1227:20 (Little); *see also* TD1 318:9-319:3 (Rabinow).

CN’845 Examples

	EX. 1	EX. 2	EX. 3	EX. 4	EX. 5	EX. 6	EX. 7*	EX. 8*	CLAIMS
Aprepitant	0.5%	2%	0.05%	0.5%	2%	0.5%	0.115%	0.06%	0.7%
Emulsifier	3% egg yolk lecithin	10% poloxamer	6% polysorbate	6.5% egg yolk lecithin	10% egg yolk lecithin	0.5% egg yolk lecithin	~5.6% egg yolk lecithin	~0.6% PEG – caprylic acid glyceride	14% egg yolk lecithin
Oil	30% soybean oil	5% ethyl oleate	6% peanut oil	15% soybean oil	20% soybean oil	15% soybean oil	~5.5% soybean oil	~0.6% olive oil	9-10% soybean oil
Sodium Oleate	–	–	–	–	–	–	–	–	Any amount as a pH modifier
pH	7.2	6.8	8.0	–	6.8	7.2	~8.0	~7.2	7.5 – 9.0
Protective Agent	5% glycerin	20% sucrose	5.95% glucose	8% glycerin	5% glycerin	5% glycerin	~0.6% glycerin	~0.5% xylitol	5% sucrose
Co-Emulsifier	1.5% ethanol	3% glycerol	2% polyethylene glycol 400	1% ethanol	3% ethanol	10% ethanol	~3.2% ethanol	~0.6% 1,2-propanediol	2-6% ethanol

* Calculated values displayed for Examples 7-8, which included a dilution step where an aliquot is diluted to a larger volume

JTX-71 at .0014 – .0017

PDX4-4

Dr. Rabinow worked backwards from the claims, picking and choosing his preferred disclosures.

Staring down this broad, unsupported disclosure, a POSA would have also been aware that the same scientists behind CN ’845 had also published Zhou the following year. TD4 1253:2-9 (Little); *see also* TD1 190:2-5, 313:13-20, 321:4-20 (Rabinow); DDX1-3. Through pre-experimental and single factors analysis, the authors determined which ingredients and ranges to conduct an orthogonal test to determine the “optimal formulation” from their work. TD4 1254:4-24 (Little); JTX-115.1, .7, .9. Zhou reported “[t]he optimal formulation” for an emulsion of 0.25 % aprepitant that would maximize one measure of stability—the centrifugal stability constant (K_e)—contained 2.5% egg lecithin and 15% soybean oil.[11] JTX-115.1, .6-7.

Taking egg lecithin as an example, Zhou steered towards the low single digit concentrations of emulsifier that had already become the industry standard, and which other

[11] K_e is not one of the three measures of “physical stability” required to satisfy the Court’s construction, nor does Zhou include any PFAT5 or crystallization data. TD1 325:18-326:1, 330:17-20 (Rabinow); TD4 1324:4-10 (Little); *see also supra*, § II.C.2 (showing in Example 5 of the patents-in-suit that Zhou’s optimized formulation was not actually physically stable).

prior-art references like Hingorani continued to use even after publication of CN ’845. TD4 1285:21-1286:10 (Little), JTX-115.1, .9; TD1 258:12-259:19, 262:13-263:21, 327:25-328:8 (Rabinow); JTX-21.8; *see also* TD1 306:3-11; DDX1-3.[12] While Dr. Rabinow paid lip service to references like Zhou and Hingorani, he ignored their actual teachings (using lower amounts of emulsifier) and instead unduly focused on the outdated disclosure of 10% emulsifier from the range in CN ’845, which contained no stability data (TD1 189:7-14 (Rabinow)), and arbitrarily going higher from there.

Dr. Rabinow tried to justify his continued focus on CN ’845 by calling it a “game changer” that “transformed the state of the art” and that “up until that point, the conventional wisdom was that emulsions . . . were appropriate for drugs that were oil soluble,” but CN ’845 formulated an emulsion with a drug that is insoluble in both water and oil (aprepitant). TD1 132:21-133:15, 326:2-4 (Rabinow). Dr. Rabinow contended a POSA would have thought that CN ’845 taught that the aprepitant in its formulations formed a “complex” with egg lecithin that stabilized the emulsion. TD1 181:24-182:5 (Rabinow).[13] But the evidence, including its own author’s (Zhou’s) superseding work, and the fact that neither CN ’845 nor Zhou even mention complexation, shows that CN ’845 was far from the “game changer” that Dr. Rabinow asserted. TD1 354:16-19, 355:2-4, (Rabinow); *see also* TD1 181:20-23 (Rabinow) (“Q. Did the CN ’845 reference show data that a complex was being formed within the reference itself? A. No.”).[14] Complexation is simply not

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[12] The background section of Hingorani stated that “to the best of the inventors’ knowledge, no such soluble and stable formulation of aprepitant has been reported.” TD1 262:2-10 (Rabinow); JTX-21.2 (¶ 9).

[13] Dr. Rabinow, however, asserted that emulsions had been used on drugs that were not soluble in water or oil since at least the mid-1990s (TD1 171:14-172:1, 360:21-361:5; JTX-113.1, .9), and complexation with phospholipids had been disclosed since at least 1990 (TD1 178:2-180:1; JTX-74.1 (claiming priority to Feb. 9, 1990)).

[14] In fact, despite asserting every example in CN ’845 was physically stable (TD1 349:8-13

a feature of CN ’845. TD4 1228:9-19 (Little).

And Dr. Rabinow never identified any other art that even discusses CN ’845, let alone describes it as a “game changer.” TD1 326:2-18 (Rabinow). Drs. Little and Hale likewise did not hear about CN ’845 when it published despite being experts in the relevant field at the time. TD3 954:14-956:9 (Hale); TD4 1244:1-1245:19 (Little). Moreover, Dr. Rabinow provided no testimony that he learned of CN ’845 outside of this litigation. Indeed, Dr. Rabinow formed his opinions only *after* reviewing Fresenius’s claim charts and invalidity contentions. TD1 344:9-345:18 (Rabinow). This evidence hardly supports the premise that CN ’845 “transformed the state of the art” (TD1 132:21-25 (Rabinow)), let alone with respect to complexation.

Moreover, even if Dr. Rabinow were right that CN ’845 were a “game changer”—which it was not—then the last thing a POSA would do would be to change the game again away from the upper limit of the broad emulsifier range identified in CN ’845, *i.e.*, 10 wt/wt %, instead of working within it.[15] *See Eisai Co. Ltd. v. Dr. Reddy’s Lab’ys. Ltd.*, 533 F.3d 1353, 1358 (Fed. Cir. 2008) (“The record, however, shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property.”).

In sum, Dr. Rabinow focused on CN ’845 only ***after*** reviewing the Asserted Claims and Fresenius’ invalidity contentions—and his resulting bias is clear. TD1 344:9-345:18 (Rabinow). He provided no basis other than hindsight for focusing on CN ’845 (*i.e.*, with its broadly disclosed ingredient ranges, such as 0.5 to 10% egg lecithin, unsubstantiated by any data) over Zhou (*i.e.*,

(Rabinow)), Dr. Rabinow admitted that at least one example in CN ’845 cannot even form a complex. TD1 350:7-352:15 (Rabinow). And, Dr. Rabinow did not provide a theory for how other examples in CN ’845, which did not contain egg lecithin, could undergo complexation. TD1 354:12-15; *see* JTX-71.15 (Examples 2 and 3); JTX-71.17 (Example 8); *see also infra* § IV.E.2.

[15] Moreover, the very same authors took the opposite course in Zhou, which optimized its egg yolk lecithin concentration to an amount at the lower end of the range disclosed in CN ’845, *i.e.*, 2.5%.

the same researcher's follow-on work that arrived at a single optimized formulation with just 2.5% egg lecithin) and Hingorani (*i.e.*, which used the conventional prior-art amount of ~1% egg lecithin despite post-dating CN '845). TD1 318:9-11 (Rabinow), TD4 1245:20-23 (Little).[16]

2. Fresenius Failed to Prove That a POSA Would Have Been Motivated to Use 14% Egg Lecithin in Combination with the Remaining Claim Limitations

There was no evidence at trial that CN '845, Zhou, or any other aprepitant-emulsion prior art disclosed or suggested aprepitant emulsions with 14% egg lecithin. (TD1 324:8-11, 331:2-13 (Rabinow); TD4 1223:25-1224:3, 1257:10-14 (Little).)

To look for numbers higher than 10% with the benefit of hindsight knowledge of the invention, Dr. Rabinow reached into the field of microemulsions (*i.e.*, Liu) and noted a generic reference to 5-30% surfactant. In doing so, Dr. Rabinow ignored that microemulsions are a thermodynamically distinct class of formulations with entirely different formulation properties and compositions. *See infra*, § IV.E.2.b. Dr. Rabinow also raised theoretical discussions of drug-phospholipid complexation to then argue that CN '845 involved (though did not desribe) aprepitant complexing with egg lecithin. *See infra*, § IV.E.2.c. As discussed below, Fresenius failed to prove by clear and convincing evidence that a POSA would have found motivation to combine such disparate references with CN '845, or that a POSA doing so would have obviously arrived at the claimed invention, or that such a POSA would have had a reasonable expectation of

[16] Indeed, with no experimental data, Dr. Little explained how statements in CN '845 would raise questions about what work was actually done. These included typographical errors that would have left a POSA guessing as to the actual volumes and pressures that were used in preparing the emulsions, to the use of the technical term "microemulsion" when the formulations were not microemulsions, and to formulation instructions that leave a POSA to fill in gaps without guidance. *See* TD4 1233:9-1235:2, 1236:11-1243:23 (Little). Moreover, CN '845 never materialized into an issued patent, failed to pair any actual stability data with its incommensurately broad disclosures, never resulted in an actual product, and did not result in a stable formulation when followed in Example 4 of the patent-in-suit. *See, e.g.*, TD4 1322:21-1326:1, 1435:13-21 (Little).

success.

a. CN ’845 and Zhou Disclose a Maximum of 10% Egg Yolk Lecithin and Optimize to 2.5%

CN ’845 disclosed a range of 0.5-10% emulsifier. TD1 331:2-6 (Rabinow); TD4 1223:25-1224:3 (Little). Subsequently, Zhou disclosed that the “optimized” formulation of aprepitant emulsion had 2.5% egg yolk lecithin. TD1 323:20-324:7, 328:24-329:4, 349:2-7 (Rabinow); TD4 1257:10-14 (Little); JTX-115.1.

Focusing on the emulsifier ranges that best fit his narrative, Dr. Rabinow conveniently ignored the disclosures in CN ’845 and Zhou that are inconsistent with his opinions. The examples in CN ’845 and the “optimized” formulation in Zhou—which Dr. Little depicted at trial in his demonstratives PDX4-4 and PDX4-5, reproduced below—show the heterogeneity of the disclosed ingredients and amounts in these documents’ examples. Dr. Little’s demonstrative PDX4-4 took a closer look at the actual ingredients and amounts in the CN ’845 examples:

CN’845 Examples

	EX. 1	EX. 2	EX. 3	EX. 4	EX. 5	EX. 6	EX. 7*	EX. 8*	CLAIMS
Aprepitant	0.5%	2%	0.05%	0.5%	2%	0.5%	0.115%	0.06%	0.7%
Emulsifier	3% egg yolk lecithin	10% poloxamer	6% polysorbate	6.5% egg yolk lecithin	10% egg yolk lecithin	0.5% egg yolk lecithin	~5.6% egg yolk lecithin	~0.6% PEG – caprylic acid glyceride	14% egg yolk lecithin
Oil	30% soybean oil	5% ethyl oleate	6% peanut oil	15% soybean oil	20% soybean oil	15% soybean oil	~5.5% soybean oil	~0.6% olive oil	9-10% soybean oil
Sodium Oleate	–	–	–	–	–	–	–	–	Any amount as a pH modifier
pH	7.2	6.8	8.0	–	6.8	7.2	~8.0	~7.2	7.5 – 9.0
Protective Agent	5% glycerin	20% sucrose	5.95% glucose	8% glycerin	5% glycerin	5% glycerin	~0.6% glycerin	~0.5% xylitol	5% sucrose
Co-Emulsifier	1.5% ethanol	3% glycerol	2% polyethylene glycol 400	1% ethanol	3% ethanol	10% ethanol	~3.2% ethanol	~0.6% 1,2-propanediol	2-6% ethanol

* Calculated values displayed for Examples 7-8, which included a dilution step where an aliquot is diluted to a larger volume

JTX-71 at .0014 – .0017

PDX4-4

PDX4-4; *see also* TD4 1220:2-1223:24 (Little). As shown above, Example 1 in CN ’845 used 3% egg lecithin. Examples 2 and 3 did not use any egg lecithin, but poloxamer and polysorbate 80.

And, the sole example that had between 8-10% egg lecithin in the final solution (Example 5), had a different amount of aprepitant (2%), a different amount of soybean oil (20%), a different pH (6.8), no sodium oleate, and no sucrose as compared to the Asserted Claims.[17] *See* PDX4-4; TD4 1220:2-1222:15 (Little). Moreover, as discussed above (*see* §§ II.C.2, IV.E.1), CN '845 disclosed no stability data, including for any of its examples, and when the Heron inventors used 9.95% egg lecithin to test a CN '845 formulation themselves in Example 4 of the patents-in-suit, it was not stable—aprepitant crystals formed within four days at room temperature. *See* JTX-1.14-16.

The "optimized" aprepitant emulsion in Zhou, also contained significantly less egg lecithin (2.5%) than the Asserted Claims (14%):

Zhou Compared to the Asserted Claims

	Optimal Zhou Formulation	Claims
Aprepitant	0.25 %	0.7 %
Emulsifier	2.5 % egg yolk lecithin	14 % egg yolk lecithin
Oil	15 % Soybean oil	9 – 10 % Soybean oil
Sodium Oleate	–	Any amount as a pH modifier
pH	7.31 ± 0.30	7.5 – 9.0
Protective Agent	–	5 % sucrose
Co-Emulsifier	Removed	2 – 6 % ethanol
	Oleic acid	

JTX-115 at .0001, .0006 – .0007

PDX4-5

[17] Example 7 of CN '845 also does not contain 8-10% egg lecithin because it describes a final dilution step with normal saline that results in the concentrations shown in PDX4-4, including only about 5.6% egg lecithin. TD4 1222:25-1223:24, 1335:3-13 (Little). Regardless, even the intermediate pre-dilution solution contained a significantly different formulation than the Asserted Claims, included a lower concentration of egg lecithin (9.8%) no sodium oleate, and no sucrose. TD4 1222:25-1223:24, 1335:5-21 (Little); JTX-71 (¶ 32). Through a confusing cross-examination, Fresenius attempted to misleadingly imply that these examples are nonetheless within the claimed ranges. *See* TD4 1357:4-1362:6 (Little). Fresenius also questioned Dr. Little regarding the dilution step in an effort to read in the existence of a product for injection before the dilution step, but that is simply not correct. TD4 1354:23-1371:25 (Little).

PDX4-5; TD4 1247:15-1249:19 (Little). And, as discussed above in Section II.C.2, Heron's inventors also tested the optimized Zhou formulation with 2.5% egg lecithin, and reported in Example 5 of the patents-in-suit that it too was unstable. *See* JTX-1.15-16.

b. Dr. Rabinow Improperly Relies on Liu to Increase Lecithin Above 10%

Instead of working within the amount of emulsifier in CN '845 and Zhou, without any support, Dr. Rabinow asserts that a POSA would look to the mention of the words 5-30% in Liu for surfactant, ignoring what Liu in fact was discussing—a system known as "microemulsions." TD1 228:15-20 (Rabinow). This unexplained reliance not just on another reference, but one for a different formulation system altogether, conflicts with Dr. Rabinow's opinions for the other claimed ingredients. For aprepitant, oil, co-emulsifier, protective agent, and pH, Dr. Rabinow asserted that a POSA would simply work from the ranges disclosed in CN '845. TD1 227:18-228:14 (Rabinow). Yet, for the amount of emulsifier—and only for the amount of emulsifier—Dr. Rabinow improperly asserted that a POSA would work from the distinct formulation systems of Liu. TD1 228:15-20 (Rabinow).

In addition, the range of 5-30% surfactant in Liu would ***exclude*** the emulsifier amount used in Examples 1, 6, and 8 in CN '845 (which contain less than 5% emulsifier) (TD4 1220:2-1221:5 (Little); PDX4-4; JTX-71.14-17), all the Examples in Hingorani (which contain about 1% egg lecithin) (TD1 327:25-328:2 (Rabinow); TD4 1286:2-7 (Little); JTX-21.8), and even the optimized formulation in Zhou (which contains 2.5% egg lecithin) (TD1 323:20-324:7, 349:2-7 (Rabinow); TD4 1257:10-14, 1286:8-10 (Little); JTX-115.1, .7, .9-10). It would likewise exclude the FDA-approved intravenous emulsions (which all use 1.2% egg lecithin) (TD1 327:5-9 (Rabinow)) and every emulsion Dr. Rabinow identified for which there was any stability data at all (which used no more than 3% egg lecithin) (TD4 1283:17-24 (Little); JTX-112.35-39).

The reason for this is simple: the microemulsions of Liu are distinct from the emulsions described in either CN ’845 or Zhou. TD1 162:2-24, 340:4-16 (Rabinow); TD4 1240:19-1241:16, 1289:13-1290:24, 1298:19-1299:5 (Little). Dr. Rabinow admitted that microemulsions are “not what we’re dealing with here” in CN ’845, which “obviously” does not disclose forming microemulsions.[18] TD1 162:2-24 (Rabinow). Microemulsions differ in many ways from emulsions, including because they—unlike emulsions—are thermodynamically stable. TD1 162:2-24, 340:4-16 (Rabinow); TD4 1240:19-1241:16, 1298:19-1299:5 (Little). This means that stability-related design constraints that a POSA would consider for emulsions do not apply in the same way to microemulsions, which “just naturally thermodynamically snap together.” *See* TD4 1301:25-1302:12 (Little); TD1 340:4-16 (Rabinow). Because of these differences in thermodynamic stability, a POSA would not have relied on microemulsion art like Liu for a motivation to modify an emulsion like CN ’845. *See* TD4 1288:20-1302:12 (Little).[19]

There are still more differences that make Dr. Rabinow’s mixing-and-matching of disclosures inappropriate. Among other things, microemulsions use different ingredients in different amounts than emulsions. For example, microemulsions use different oils and different amounts of oil than emulsions. TD4 1292:6-1293:7 (Little). Microemulsions also use different emulsifiers (*e.g.*, Solutol HS15) or blends of emulsifiers (*e.g.*, Solutol HS15 blended with soy lecithin). *See* TD1 342:25-343:20 (Rabinow); TD4 1289:13-1290:24 (Little); JTX-93.11. Dr. Rabinow did not identify a single example of a microemulsion that contains egg lecithin, much

[18] While the translation of CN ’845 uses the word “microemulsion,” it is undisputed that a POSA would understand it does not disclose microemulsions. TD1 190:15-21 (Rabinow); TD4 1240:19-1241:16, 1298:19-1299:5 (Little).

[19] Dr. Rabinow said that there may be “a continuum” between emulsions and microemulsions (TD2 460:25-462:8 (Rabinow)), but identified no support for this assertion.

less one with 14%. TD1 337:13-17, 338:2-9, 343:9-20 (Rabinow); TD4 1294:4-7 (Little). In fact, Liu states that after selecting the appropriate surfactant (*i.e.*, emulsifier) type, formulation optimization should be carried out to ***minimize*** its dosage. JTX-93.12; *see also* JTX-112.32 (Wan) (¶ 263) (saying "lower % of Solutol gives better results" in microemulsions). In other words, to the extent a POSA would have made formulation changes based on Liu (an incorrect premise that Fresenius fails to prove), it would not have been to make the hindsight-based increase in egg lecithin content that Fresenius suggested. TD4 1295:10-24 (Little).

When asked what concentration would an emulsifier start destabilizing an emulsion, Dr. Rabinow relied on Liu for his opinion that this would not occur before 30% emulsifier. TD1 249:18-252:1 (Rabinow). Dr. Rabinow's reference to Liu was misleading because, as stated above, microemulsions are thermodynamically stable. And, as described in Section IV.D.3.e, the prior art showed that the concentration at which additional emulsifier can destabilize an emulsion is much lower than Dr. Rabinow let on—indeed, even exceeding 0.5% emulsifier could destabilize some emulsions. *Infra* Section IV.D.3.e.

On cross examination, Dr. Rabinow could not save this hindsight use of Liu by saying that safety of excipient amounts used in microemulsions can inform emulsions. *E.g.*, TD1 340:17-25, 341:24-342:11 (Rabinow). Even if this were true, it would have nothing to do with Dr. Rabinow's argument that a POSA would increase the emulsifier to achieve a stable product. As Dr. Rabinow acknowledged, "thermodynamic stability has nothing to do with safety." *Id.* There is simply nothing that can be taken from Liu and applied to CN '845 or Zhou regarding physical stability, and Dr. Rabinow's reliance on Liu for the mention of a range of generic surfactant (a range found nowhere in the emulsion art) is wrong and not credible. TD4 1289:13-1290:24, 1298:19-1299:5, 1301:20-1302:12 (Little).

Finally, although Liu does not mention egg lecithin, it does disclose that the use of phospholipids (a class that includes egg lecithin) would be suitable for a ***water-in-oil*** microemulsion system. JTX-93.11-12; TD4 1291:2-20, 1299:6-1301:5 (Little). Even if that were an emulsion, it would be the exact opposite of the ***oil-in-water*** emulsion system described in CN '845, Zhou, and the patents-in-suit. *See* TD4 1291:2-20, 1299:6-1301:5 (Little); *see also* TD1 13:1-13 (Little). Simply put, Fresenius has not identified anything in Liu (or any other prior art) that discloses departing upwardly from the ranges disclosed in CN '845, in a direction opposite to Zhou's optimization of CN '845.

c. Dr. Rabinow's Failed to Prove His Complexation Theory Would Have Motivated a POSA to Increase Lecithin Percent

Dr. Rabinow argued that CN '845 involved aprepitant complexing with emulsifier, which a POSA would have viewed as a reason to increase the amount of emulsifier over that of CN '845 itself. TD1 181:24-182:5, 348:17-21 (Rabinow). But CN '845 does not mention complexing, let alone provide any data showing it occurred. TD1 181:20-23, 354:16-19 (Rabinow).

Dr. Rabinow even went so far as to say that all the purportedly stable aprepitant emulsions he had seen in the prior art had complexation, which would include not just CN '845, but also Zhou and Hingorani. TD1 346:8-348:21, 366:5-19 (Rabinow). This cannot be reconciled with Dr. Rabinow's testimony that every example in CN '845 was physically stable (TD1 349:8-13 (Rabinow)) and at least Example 6 in CN '845 did not sufficiently complex with aprepitant (TD1 350:7-352:15 (Rabinow)). Similarly, CN '845 states that a variety of emulsifiers can be used, including nonionic emulsifiers like polysorbate 80 and poloxamer, and includes examples of formulations that contain these nonionic emulsifiers and no egg lecithin. TD1 354:12-15 (Rabinow); TD4 1231:13-1232:20 (Little); JTX-71.15 (Examples 2 and 3), JTX-71.17 (Example 8). These nonionic emulsifiers are very different chemically compared to egg lecithin, and Dr.

Rabinow provided no evidence or rationale as to why a POSA would have thought these emulsifiers complex with aprepitant. Altogether, even according to Dr. Rabinow, at least half of the examples in CN ’845 either do not have sufficient egg yolk lecithin to complex with aprepitant or have a totally different emulsifier than egg lecithin.

Dr. Rabinow also attempted to rely on documents showing lecithin complexes with other drugs, but these documents—Agarwal, Yue, and EP ’279—contradict, rather than support, his opinions. None mentions aprepitant (TD1 357:15-17 (Rabinow)) or disclose intravenous formulations (TD1 357:18-358:5 (Rabinow); TD4 1305:23-1306:5 (Little)), and the drugs they do mention have totally different chemical structures than aprepitant (*e.g.*, TD4 1304:2-1305:19 (Little); *see also* TD1 178:2-179:5, 180:2-13, 180:23-181:5 (Rabinow)). Moreover, each of those documents “talk about a ratio of lecithin to the active ingredient of ***3:1 or less***.” TD1 356:10-14 (Rabinow); *see also* TD4 1306:13-20 (Little). In contrast, the Asserted Claims use 14% egg lecithin in a ratio of egg lecithin to aprepitant of ***20:1***. TD1 330:10-13 (Rabinow). Accordingly, a POSA would not increase the amount of lecithin based on these references. TD4 1302:13-19, 1304:2-1305:19 (Little).

Additionally, Dr. Rabinow failed to show why complexation would motivate a POSA to add more than the amount disclosed in CN ’845, let alone more than the (much lower) conventional amount of egg lecithin. As noted above, Dr. Rabinow stated that Zhou already achieved complexation with just 2.5% egg lecithin, and the actual complexation prior art had no more than a 3:1 ratio of lecithin to drug. What, then, would a POSA’s motivation have been to add more? There would be none. *See Janssen Pharms., Inc. v. Tolmar, Inc.*, No. 21-1784, 2024 WL 834762, at *20 (D. Del. Feb. 26, 2024) (claims not obvious “[i]n the absence of a reason to modify”) (citing *InTouch Techs., Inc. v. VGo Commc’ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014)); *see also Leo*

Pharm. Prod., Ltd. v. Rea, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013) (invention was not obvious where a stability problem was not recognized or known, so there was no motivation to modify).

d. Dr. Rabinow Incorrectly Relies on Washington to Increase Lecithin Percent

Dr. Rabinow attempted to overcome the clear deficiencies in his testimony by relying on Washington to assert that a POSA would want to increase the surface area of oil in the emulsion by increasing the amount of emulsifier at the interface. *See* TD1 173:19-174:12, 360:12-20; 364:8-365:21 (Rabinow). Washington, however, contradicts Dr. Rabinow's conclusion that a POSA would be motivated increase the amount of egg lecithin in an aprepitant emulsion. Washington gives only S-emopamil as an example of a drug that "interact[s] strongly with the emulsifier film" and is "preferentially located at the interface," and Dr. Rabinow contended that aprepitant would behave exactly the same way. JTX-113.2; TD1 361:15-362:12 (Rabinow); TD4 1306:21-1307:6 (Little). Yet, the formulations in Washington used the conventional amount of egg lecithin, 1.2%, for emulsions containing 2% of the drug. JTX-113.2, .11; TD1 364:8-365:21 (Rabinow). A POSA would have in turn find no meaningful motivation in Washington to depart from the conventional amount of emulsifier, let alone to use over five times as much. *See* TD4 1425:14-1426:13 (Little).

e. A POSA Would Not Simply Increase Emulsifier Because That Can Destabilize an Emulsion

More fundamentally, the experts agreed that there was no general rule that, the more emulsifier, the more stability. *See* TD1 249:18-252:1 (Rabinow); *see also* TD1 331:23-336:17 (Rabinow); TD4 1286:14-1288:13 (Little). For example, Dr. Rabinow agrees that there is a point at which "the amount of emulsifier clearly becomes counterproductive." *Id*. Dr. Rabinow explained that the Khan review article on pharmaceutical emulsions "deals with this" amount of emulsifier. TD1 249:18-252:8 (Rabinow). Khan, however, reports that "[a]t high emulsifier concentration emulsion instability occurs because of rapid coalescence" citing a study showing

that even 0.5% emulsifier can destabilize some emulsions. TD4 1286:14-1288:13 (Little); *see also* JTX-91.5; JTX-79.4.[20] Yet, without citing any evidence on emulsions, Dr. Rabinow asserted that a POSA could use up to 30% emulsifier. *Supra* Section IV.E.2.b; TD1 249:18-251:25 (Rabinow).

According to Dr. Rabinow, the upshot of the prior art is that "people are instructed to determine the optimal concentration window," such that "you identified what is too low a level and what is too high a level." TD1 332:2-11 (Rabinow). He also said that "the take-home lesson is that every system is different, it's independent, you got to test yourself and you determine for that system what is the appropriate concentration window." TD1 250:21-14 (Rabinow).

What Dr. Rabinow ignores is that for the aprepitant emulsion "system" in particular, the scientists behind CN '845 and Zhou already considered a broad range of emulsifier amounts from at least 0.5 to 10% and determined that the optimal formulation was 2.5%. *See supra* § IV.E.2.a. Zhou's finding also comports with ***every*** other prior-art emulsion for which stability data was actually reported having either about 1% emulsifier or no more than 3%. *See supra* § IV.E.2. Dr. Rabinow's suggestion that, despite the clear teachings of CN '845 and Zhou, a POSA would seek to use egg lecithin concentrations over 10%—and perhaps even as high as 30%—flies in the face of what Dr. Little explained is "a general principle that we have in formulation sciences, which is that, first of all, you never add something unless you have to[, a]nd, second of all, when you add

[20] Dr. Rabinow's analogy of emulsions to people using life jackets to help float on the ocean's surface actually helps illustrate in layman's terms why a POSA would have been concerned that excess emulsifier would destabilize the emulsion. TD1 177:7-178:1 (Rabinow). The life jackets represented emulsifier, the ocean represented an oil droplet in an emulsion, and the air represented the water phase of that emulsion. *Id.* Working from this analogy, Dr. Little explained that if an emulsion has 14% emulsifier and 9-10% oil (like the Asserted Claims), you would have a greater mass of life jackets than ocean—a geometric impossibility if the emulsifier is to project into both phases as Dr. Rabinow said. TD4 1228:15-1231:12 (Little); TD1 134:19-135:12 (Rabinow). Instead, the excess emulsifier disperses into the actual oil and water phases, where it could have unintended effects, such as causing destabilization, even to the point of deemulsification. *Id.*

something, you want to add it to the smallest amount that you can." TD4 1286:14-1288:13. Rather, in keeping with these principles, Dr. Little explained that, "[a]s a formulation scientist, . . . you're trying to decrease [emulsifier content], to get the lowest amount that you can for [the emulsion] to be stable." *Id.* Dr. Rabinow is simply using hindsight in imagining the POSA increasing the emulsifier higher than the upper range of CN '845, and does so using 14%, while also making no other changes.

Dr. Rabinow's contrary testimony once again begs the question: If Zhou already teaches a POSA a stability-optimized aprepitant emulsion as Dr. Rabinow (incorrectly) contends, why would a POSA seek to optimize it further, let alone by making formulations with over five times more egg lecithin (*i.e.*, 14%)? The answer is that a POSA would not. TD4 1286:14-1288:3. *See Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1272-73 (Fed. Cir. 2018) ("[The] mere fact that the prior art could be . . . modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.").

* * *

In sum, the documents that Fresenius cites do not disclose or suggest the use of 14% egg lecithin in an intravenous emulsion. As stated above, none of CN '845, Zhou, or Hingorani discloses that amount. Instead, CN '845 set a limit of 10% emulsifier, Zhou disclosed the same researcher's later "optimized" formulation with just 2.5% egg lecithin, and all of the examples in Hingorani that post-dated publication of CN '845 used about 1% egg lecithin. A POSA would not have combined any of the cherry-picked disclosures from the other, inapposite references cited by Dr. Rabinow with CN '845 or Zhou, nor would any such combination, if it were to occur, have resulted in a POSA making an aprepitant emulsion with 14% egg lecithin.

Making matters worse, while Dr. Rabinow utters the mantra of "routine optimization," he

offers no evidence showing why a POSA would have even tested the particular solution of 14 wt/wt % egg lecithin as optimization. TD1 223:1-14 (Rabinow). *See Unigene Lab'ys, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011) ("To render a claim obvious, prior art cannot be 'vague' and must collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution."). Indeed, Zhou engaged in optimization and that resulted in 2.5%.

3. Fresenius Failed to Prove That a POSA Would Have Been Motivated to Use Sodium Oleate as a pH Modifier

Dr. Rabinow made a number of arguments about why, in his opinion, CN '845 and Zhou disclose the use of sodium oleate in an aprepitant emulsion—but the fact is they do not. Dr. Rabinow admitted that CN '845 does not mention sodium oleate or oleic acid. TD1 393:5-8 (Rabinow); TD4 1216:7-17, 1219:2-4, 1252:11-1253:1 (Little). Rather, he said "[a] POSA would know that he could use sodium oleate" because of the general references in CN '845 to a pH adjuster. TD1 227:18-228:14 (Rabinow). But Dr. Rabinow did not identify a single prior art document that disclosed the use of sodium oleate to adjust pH. Instead, the prior art that Dr. Rabinow relied on shows that there are many pH modifiers, including conventional options such as sodium hydroxide. TD4 1219:5-13; 1309:14-25 (Little). For example, Wan discloses only sodium hydroxide as an example of a pH modifier (JTX-112.23 (¶ 136)), and Hingorani discloses sodium hydroxide as the preferred pH modifier for increasing pH (JTX-21.5 (¶ 32)). Additionally, sodium oleate is a weak base. Fresenius failed to prove that a POSA would have been motivated to select a weak pH modifier over a strong one, much less sodium oleate over other conventional pH modifiers. TD4 1309:9-1310:23, 1416:18-1417:16 (Little).

Dr. Rabinow also argued that CN '845 disclosed the use of sodium oleate because oleate would be present as a result of degradation of soybean oil and egg lecithin, and "sodium is everywhere" as a contaminant. TD1 159:15-160:5, 198:6-15, 378:14-17 (Rabinow). The oleate

to which Dr. Rabinow refers is part of a larger molecule and chemically bonded to a triglyceride group (in the case of soybean oil) and a glycerol group (in the case of lecithin). JTX-84.1-2. Dr. Rabinow provided no evidence that these molecules break apart to free these groups, much less that it occurs in a meaningful amount to adjust pH. As for Dr. Rabinow's argument that "sodium is everywhere," he provided no evidence that sodium would be present as a contaminant in any amount in the relevant emulsions, much less a meaningful one. TD1 378:5-21 (Rabinow).

Dr. Rabinow also argued that a POSA would have been motivated to select sodium oleate because Zhou reported that oleic acid was used as a co-emulsifier. TD1 198:19-200:4 (Rabinow). First, Zhou does not disclose the use of sodium oleate, but its conjugate acid, oleic acid. JTX-115; TD1 393:9-12 (Rabinow). This difference is significant, as the patents-in-suit describe sodium oleate as a pH modifier, which increases pH, whereas oleic acid decreases pH. TD4 1249:11-19 (Little). Second, Dr. Rabinow did not provide any basis for why a POSA would prefer to use sodium oleate as a co-emulsifier over ethanol, much less why they would include both together. Indeed, Dr. Rabinow asserted that a POSA would have been motivated to use ethanol as a co-emulsifier. TD1 147:19-148:13 (Rabinow). And, CN '845 also provided a number of other co-emulsifiers that did not include sodium oleate or oleic acid. TD1 147:13-18 (Rabinow).

The other prior art that Dr. Rabinow asserted discloses emulsions containing sodium oleate, Wan and Jumaa, show that it presents a risk of hemolysis (*i.e.*, killing red blood cells). As Dr. Rabinow agreed, "Wan concluded that the sodium oleate that was included in the formulations caused the hemolysis." TD1 318:2-5; 385:10-13 (Rabinow); TD4 1311:7-1312:1 (Little); JTX-112. Jumaa called sodium oleate a "highly lytic agent" and showed that sodium oleate caused hemolysis. JTX-88.2-3 (Figure 1.). This can be seen in Jumaa and Wan where emulsions with 0.3% sodium oleate had a hemolytic effect. TD1 455:5-8 (Rabinow); JTX-88.2-3; JTX-112.38.

Dr. Rabinow has provided no explanation for why a POSA seeking to develop an intravenous NK-1 receptor antagonist with minimal side effects would have introduced sodium oleate. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1345-46 (Fed. Cir. 2013) (prior art teaching of toxicity counts against finding a motivation to make that change). This is especially true for supportive care drugs, like those for CINV, where the tolerance for any safety concerns is extremely low. TD3 1039:20-1040:11 (Roeland).

Finally, Dr. Rabinow's reliance on Fell is improper. *See* TD1 206:10-208:1 (Rabinow). Fell is not prior art and the single, oblique reference to sodium oleate in Fell is not a reflection of the prior art. TD2 394:1-395:1 (Rabinow). Fell says only that, "[i]n addition to the phospholipid emulsifier, sodium oleate is added as a stabilizing agent and glycerin is added as an osmotic agent." JTX-76.4. Fell provides no citation for this statement available to a POSA in 2014, does not explain what the formulation is, and does not state whether any such formulation was tested in animals. *Id.* Dr. Rabinow also failed to prove that a POSA would have been motivated based on this non-prior art discussion to use sodium as a pH modifier in the claimed aprepitant emulsion.

4. Fresenius Failed to Prove That a POSA Would Have Been Motivated to Use the Other Claimed Ingredients and in the Claimed Amounts

Instead of working from any actual formulation that was disclosed in the prior art, Dr. Rabinow went to the broadest disclosures in CN '845 and picked and chose from among those lists of ingredients and their ranges trying to line them adup with the claims, not whether a POSA would have actually had a motivation to use these various formulation aspects together as a whole. He then modified the generic ranges. This is improper. *See ModernaTx, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1364, 1376 (Fed. Cir. 2021) ("[P]rovid[ing] evidence of general considerations to be taken into account with respect to each individual component" was insufficient to prove obviousness of multi-component claims because the "evidence failed to

address the interdependence of the claimed . . . components and how adjustments would affect the [claimed invention] as a whole."); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724-25 (Fed. Cir. 1990) ("Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness."); *see also supra* § IV.E.1.

Where the disclosed range of an ingredient aligned with the Asserted Claims, Dr. Rabinow used that as the "operative range" which a POSA would use. TD1 227:18-228:20 (Rabinow) ("The oil phase is given as 5 to 30 percent, that includes the claimed levels of 9 to 10 percent."). But, where the amount of the ingredient did not fall within the range, ***and only where it did not***, Dr. Rabinow then set an "operative range" based on another, unrelated document. *Id.* For example, Dr. Rabinow set the operative range for egg lecithin based on Liu, which as discussed above was improper. *Id*. This shows hindsight.

Likewise, where the preferred ingredient lined up with the Asserted Claims, Dr. Rabinow said that a POSA would start with that preferred ingredient. TD1 144:13-148:16 (Rabinow). For example, Dr. Rabinow asserted that a POSA would have seen the preference for soybean oil in CN '845, know from their general understanding that soybean oil was the most used oil, and then start with it as a result. *E.g.*, TD1 145:9-146:5 (Rabinow). But, where the preferred ingredient did not line up, ***and only where it did not line up***, Dr. Rabinow argued that a POSA would select something from an undifferentiated list in CN '845. TD1 148:14-149:21(Rabinow). For example, although CN '845 identified the preferred protective agent as glycerin (also called glycerol), Dr. Rabinow asserted that a POSA would have selected sucrose. TD1 377:2-5 (Rabinow).

In contrast to the conventional use of glycerin,[21] Dr. Rabinow did not identify a single

[21] Strickley explained that a "***typical***" emulsion for injection contained glycerin. JTX-105.23.

intravenous emulsion containing sucrose that was FDA approved. Additionally, the prior art that Dr. Rabinow cited for aprepitant emulsions, including Zhou and Hingorani, used glycerin and not sucrose. TD1 197:21-198:5, 261:3-12, 377:7-10 (Rabinow); JTX-21.8; JTX-115.7. Dr. Rabinow also used hindsight to summarily dispose of the remaining protective agents disclosed in CN '845, thereby narrowing the list of non-preferred protective agents down to the only one that lined up with the Asserted Claims (*i.e.*, sucrose). For example, he said "you can't use glucose" even though "[g]lucose was perhaps the most used in terms of an osmotic agent in injectables" because it would not be suitable unless the pH was slightly acidic. TD1 148:20-149:15 (Rabinow). Not only does this assertion rely on Dr. Rabinow's hindsight conclusion that a POSA would disregard the lower portion of the pH range disclosed in CN '845 (pH 6.0 to 8.0), but it is outright contradicted by the fact that the example in CN '845 with glucose used the *highest* pH disclosed in CN '845 (a pH of 8.0). *Id.*; JTX-71.15. As additional example, Dr. Rabinow did not even consider xylitol, which was included in one of the examples in CN '845. *See* TD1 148:20-150:10; JTX-71.17.

Finally, that the ranges Dr. Rabinow asserted a POSA would have worked from (either from CN '845 or Liu) were available to the Zhou researchers further demonstrates his hindsight. Indeed, the Zhou researchers had virtually all of the prior art on which Dr. Rabinow relies, and they themselves identified and published the ranges and lists of ingredients in CN '845 in the first place. Still, when the Zhou researchers investigated and disclosed their specific formulations, including those in CN '845 and Zhou, ***none came remotely close to the combination of the Asserted Claims***. How then, would a POSA with at best the same information as Zhou (and in all

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Glycerin was also used in the FDA-approved intravenous emulsion called Diprivan (propofol). JTX-105.18. Additionally, while Dr. Rabinow relied on the formulation of an FDA-approved intravenous emulsion called Intralipid for his selection of egg lecithin and soybean oil (TD1 145:9-21, 146:14-125), he ignored that Intralipid contained glycerin (TD1 148:20-149:21).

likelihood less) arrive at the formulations disclosed in the Asserted Claims? A POSA would not.

F. Fresenius Failed to Prove That a POSA Would Have Had a Reasonable Expectation Success in Dr. Rabinow's Proposed Prior Art Combination

Even if, for the sake of argument, a POSA were motivated to make Dr. Rabinow's hindsight-driven, selective combination, Fresenius has failed to prove that a POSA would have had a reasonable expectation that making all of Dr. Rabinow's modifications to the formulations of CN '845 and Zhou would successfully result in a stable, intravenous formulation of an NK-1 antagonist. As an initial matter, aprepitant was widely understood to be very difficult to formulate for intravenous use (TD3 914:18-915:8 (Hale); TD4 1270:7-1271:15, 1321:6-13 (Little) (aprepitant is like "brick dust")), and an emulsion was "one of the more complex formulation strategies," so the POSA would be "adding complexity" (TD4 1321:14-20 (Little); *see also* TD4 1279:2-14 (Little)), further detracting from any reasonable expectation of success. After over 20 years of industry failure, a POSA would have been skeptical of an aprepitant emulsion being stable and safe for intravenous use. TD4 1322:21-1323:21 (Little); *see also infra* § IV.H.2.

While Dr. Rabinow asserted that the motivation to increase emulsifier is to increase stability (TD1 136:10-137:11 (Rabinow)), he did not specifically argue that a POSA would have reasonably expected that using 14% egg lecithin, sodium oleate as a pH modifier, or the entirety of the claimed combination would result in a stable aprepitant emulsion that was safe for intravenous use. *See Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F.Supp.3d 377, 421 (D. Del. 2021) (no reasonable expectation of success because a POSA would be "faced with a hodgepodge of teachings of capsules and tablets, with different excipients and different amounts").

Additionally, the prior art undisputedly showed that increasing an emulsifier could cause stability issues (*see supra* § IV.E.3.d), that adding sodium oleate to emulsions could cause hemolysis (*see supra* § IV.E.4), and that emulsions are complex systems in which changing

ingredients and their amounts could have a cascade of effects (TD4 1316:17-1318:22 (Little); TD2 474:1-14, 506:13-20, 508:1-16 (Han); TD2 547:23-548:2 (Ottoboni); TD4 1278:6-1279:1, 1321:14-20, 1426:1-13 (Little)). Even so, Dr. Rabinow makes only the conclusory assertions that a POSA "doing routine optimization" would have increased the amount of egg yolk lecithin above the 10 wt/wt % disclosed in CN '845 (TD1 301:23-302:9 (Rabinow)), would have used sodium oleate as a pH modifier (TD1 159:12-160:5, 206:4-9, 231:8-24; 425:3-8 (Rabinow)), and would have selected all the claimed ingredients and amounts. TD1 230:19-231:7, 339:14-17 (Rabinow)). This is not only incorrect (TD4 1278:6-1279:1, 1281:16-21, 1309:9-1310:23, 1316:17-1318:22, 1321:14-1322:20, 1325:20-1326:1, 1426:1-13 (Little)), but improper. *See Intendis GMBH v. Glenmark Pharms. Ltd.*, 117 F.Supp.3d 549 (D. Del. 2015), *aff'd, Intendis GMBH v. Glenmark Pharms. Inc., USA*, 822 F.3d 1355 (Fed. Cir. 2016) (finding no reasonable expectation of success because "swapping ingredients in complex chemical formulations is anything but 'routine'").

Fresenius is wrong that a POSA would have expected that increasing egg lecithin content beyond the 10% upper limit of CN '845 to 14% (*i.e.*, 40% more) would yield a physically stable aprepitant emulsion. CN '845 provides no stability data whatsoever for any of its emulsions, let alone those with the full amount of 10% egg lecithin. *Supra*, § IV.E.1. And the only stability data for CN '845 is from Example 4 of the patents-in-suit, which show that using 9.95% egg lecithin resulted in an ***unstable*** aprepitant emulsion. *Supra*, § II.C.2. Moreover, the stability-oriented optimization work in Zhou brought egg lecithin content *down* to 2.5%. *Supra*, § IV.E.2.a.

Given the physical attributes of aprepitant, the difficulty of working with intravenous emulsions that was reported in the art, the number of significant modifications that Fresenius asserts over CN '845 (and even Zhou), and the paucity of available experimental results, Fresenius failed to prove that a POSA would have had a reasonable expectation of success. TD4 1321:6-

1323:21, 1325:4-1326:1 (Little).

G. Fresenius Failed to Prove That "Criticality" is Required; Heron Anyway Proved That The Asserted Claims Meet "Criticality"

Fresenius failed to prove the predicate to its criticality argument. There is no dispute that the disclosure of 0.5-10% emulsifier in CN '845 does not overlap with 14% egg lecithin in the Asserted Claims. TD1 313:25-315:15 (Rabinow). The upper limit for emulsifier disclosed in CN '845 is 10%. TD1 331:2-18 (Rabinow). And Dr. Rabinow did not prove that difference between the amount of emulsifier in CN '845 and the amount of egg lecithin in the Asserted Claims are either not meaningful or that a POSA would know to discard the limits set by CN '845. *See In re Patel*, 566 F. App'x 1005, 1010 (Fed. Cir. 2014) (nonprecedential) ("Where differences clearly exist and there is no evidence that they are either not meaningful or one of skill in the art would know to discard the limits set by the prior art, proximity alone is not enough to establish a prima facie case of obviousness.").

Additionally, the amount of emulsifier is not the only difference between CN '845 and the Asserted Claims. And, "[w]here there are additional differences between the prior art and the patented invention, the presumption of obviousness may not be invoked." *Janssen*, 2024 WL 834762, at *43 (citing *Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006, at *9 (Fed. Cir. 2022). For example, CN '845 does not disclose sodium oleate, and Dr. Rabinow failed to prove that a POSA would have considered using sodium oleate based on the vague reference to a pH adjuster in CN '845. *Supra* § IV.E.3.

This also is not a case where the prior art disclosed just a somewhat broad range. *See Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011). Indeed, CN '845 does not disclose a range specific to egg lecithin at all. CN '845 discloses a total of five emulsifiers, along with eight oils, four co-emulsifiers, seven protective agents, an

undefined class of "pH adjusters," and a pH range of 6.0 - 8.0. JTX-71.13. And the ranges provided in CN '845 are for these categories (*e.g.*, emulsifiers) and not any particular ingredient (*e.g.*, egg lecithin). JTX-71.13. Additionally, these ranges are very broad. The amount of aprepitant can vary by 40x (from 0.05 to 2 w/wt %), the amount of emulsifier can vary by 20x (from 0.5 to 10%), the amount of oil can be anywhere from 5-30%, the amount of co-emulsifier can be anywhere from 1-10%, and the amount of protective agent can be anywhere from 5-20 %. *Id.* The vast number of permutations covered by CN '845 is illustrated by the heterogeneity of its preferred embodiments, none of which come remotely close to the Asserted Claims. *Supra* § IV.E.1. "The facts here present a case where the disclosed range is so broad as to encompass a very large number of possible distinct compositions thus requiring nonobvious invention." *See Genetics*, 655 F.3d at 1306 (affirming a district court finding that there was no *prima facie* case of obviousness based on *Peterson*).

Accordingly, there is no requirement to show criticality, since there is no showing in the first place to modify the ranges of the prior art, achieving the claimed invention and having a reasonable expectation of success. Even if it were required, the evidence shows that the Asserted Claims do in fact demonstrate criticality over CN '845. *See infra* § IV.H. And, as the patent examiner concluded, the evidence of criticality on its own provides a sufficient basis for the nonobviousness of the Asserted Claims. *See* JTX-2.162 ("Applicant has demonstrated criticality of the range in regard to the wt. / wt.% of egg yolk lecithin and the ratio of egg yolk lecithin to aprepitant, thereby overcoming any assertion of obviousness the Examiner could make based upon her review of the prior art.").

The patents-in-suit show that Example 4 (using ingredients and concentrations disclosed in CN '845) was not physically stable, while Example 2 (using ingredients and concentrations in

the Asserted Claims) was. *Supra* § II.C. Fresenius's assertion that there was just a "three-day difference" between CN '845 and the Asserted Claims is wrong. *See* D.I. 170 at 15. Example 4 was not "stable for four (4) days"—instead, crystals were observed "***within 4 days***." D.I. 170 at 15; JTX-1.15 at 18:44-46. In other words, Example 4 was not stable on Day 4, and the patents do not suggest that Example 4 was stable until then. JTX-1.15 at 18:44-46. Additionally, the examples in the patents-in-suit were physically stable for ***two to three months*** at room temperature. JTX-1.16-17 (Table 7). And, both Heron and Fresenius assert that their aprepitant emulsions can be used by patients after 60 days at room temperature and more than a year of storage at 5 °C. JTX-51.24; JTX-188.22; JTX-49.4-6, .41-43, .47-49; JTX-35.2. This is a difference of kind, not degree, as the rapid precipitation of aprepitant crystals in the prior art formulations made them unsuitable for use in patients. *See supra* § II.C.2. In contrast, the Asserted Claims provide a usable and practical drug product that can and does help patients. *See supra* § II.E.

H. Objective Indicia Further Demonstrate Nonobviousness of the Patents-in-Suit

Even without objective indicia, Fresenius failed to meet its burden of proof. The real-world evidence further supports a finding of nonobviousness of the claimed invention. Objective indicia are "essential safe-guards that protect against hindsight bias" and serve as a "fundamental part of the overall § 103 obviousness inquiry." *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1136-37 (Fed. Cir. 2019). Here, long-felt but unmet need, failure of others, unexpected results, commercial success, and copying confirm that Fresenius's obviousness allegations were tainted with impermissible hindsight. Fresenius retains the ultimate burden of proving obviousness by clear and convincing evidence, even when considering objective indicia of nonobviousness. *See, e.g.*, *In re Cyclobenzaprine*, 676 F.3d at 1078 n.5 ("[The] party challenging validity bears the burden of persuasion throughout the litigation."); *see also Immunex Corp. v. Sandoz Inc.*, 395

F.Supp.3d 366, 401 (D.N.J. 2019) ("While both parties offered evidence of objective indicia to support their positions, the burden always remains on Defendants to prove by clear and convincing evidence that the claimed invention is obvious.").

1. Long-Felt Unmet Need

Cinvanti® satisfied a long-felt but unmet need. A long-felt need arises when there is "an articulated identified problem and evidence of efforts to solve that problem." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332, 1334 (Fed. Cir. 2016); *see also Lundbeck v. Lupin Ltd.*, No. CV 18-88-LPS, 2021 WL 4944963, at *254 (D. Del. Sept. 30, 2021) (finding an unmet need for a pharmaceutical product that "could offer a better side effect profile without sacrificing efficacy"); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) (satisfying a long-felt need for a safer and more effective drug supports nonobviousness).

Before Cinvanti®, "there was a long-felt unmet need for an NK-1 receptor antagonist that was as equally efficacious [as Emend® IV (fosaprepitant)] with fewer related side effects." TD3 1058:17-1059:2 (Roeland). Intravenous NK-1 receptor antagonists are "preferentially prescribe[d]" because doctors "know that patients are going to get the drug" and that the receptors are "saturated and treated," compared to oral NK-1 receptor antagonists, about which doctors have more concerns about both patient adherence and bioavailability. *See* TD3 1017:12-1018:7, 1018:17-23, 1020:8-24 (Roeland).

In addition, such supportive care medicines—which are meant to effectively facilitate delivery of cancer treatment—should not have side effects that disincentivize their use, and thereby adversely impact the delivery of potentially lifesaving chemotherapy. TD3 1014:8-1016:10, 1039:11-1040:11 (Roeland). Thus, although there was much excitement around the approval of

Emend® IV in 2008, the industry recognized that significant ISAEs resulted from its use,[22] including thrombophlebitis, vasculitis, and necrosis. *See* TD3 1021:17-1024:7, (Roeland); TD2 714:20-715:6 (Markman); JTX-129 (Emend® IV ISAE warning); JTX-146.4 (showing ISAEs at 67% with higher concentrations of fosaprepitant); JTX-154.2 (showing ISAEs at 28% with fosaprepitant); JTX-138.5 (showing ISAEs at 15% with fosaprepitant); JTX-134.3 (showing ISAEs at 7.4% with fosaprepitant); *see also* TD3 1033:3-1035:5 (discussing reports of ISAEs ranging from 67% to 7.4%) (Roeland).

For example, the Mayo Clinic, for patients getting AC, switched back to oral aprepitant despite concerns around adherence and bioavailability because ISAEs with Emend® IV "were a prominent and substantial problem for a significant number of patients." JTX-137.2; *see also* TD3 1029:8-1033:2 (discussing Leal 2014 and observed ISAEs when using Emend® IV) (Roeland). These significant adverse events required the amendment of the Emend® IV label. *See* JTX-150.5 (Emend® IV label updated to include ISAEs); TD3 1024:15-21 (noting "a lot of the toxicities and things that we see happen over time and as we're using these drugs more and more") (Roeland).

The industry attributed these ISAEs to polysorbate 80, a surfactant known since at least 2005 to cause hypersensitivity reactions (JTX-126.1). *See* JTX-139.1; JTX-150.2; JTX-148.2; JTX-155.10; *see also* TD3 1035:6-12, 1046:20-1054:20 (Roeland). Through Dr. Markman, Fresenius asserts that there is no evidence of polysorbate 80 causing hypersensitivity reactions. *See* TD2 667:22-668:1 (Markman). The NCCN Guidelines, which provide a "statement of

[22] Dr. Markman confirmed that retrospective studies can be helpful in clinical cancer investigation because they can provide clinically relevant data in populations known to be poorly represented in cancer clinical trials and may identify adverse events potentially not recognized in the highly analogous group of study patients. TD3 726:6-17; 727:3-728:15 (Markman). Dr. Roeland further confirmed that retrospective studies are valuable, especially around toxicity studies, because they are approached with the scientific method and prospective observational studies are generally not available in symptom science. TD3 1028:2-23 (Roeland).

evidence and consensus of the authors regarding their views of currently accepted approaches to treatment," however, recognize that the polysorbate 80 in Emend® IV "may be implicated in infusion hypersensitivity reactions." *See* JTX-142.28; *see also* TD2 732:18-733:4 (agreement with goal of NCCN Guidelines) (Markman). Even Fresenius's expert, Dr. Rabinow, agrees that polysorbate 80 had "known problems," was associated with "some allergic type reactions," and a POSA would therefore like to see development of an injectable NK-1 that "did not contain the polysorbate 80." TD1 122:21-123:7, 125:17-126:5, 147:1-12 (Rabinow).

Dr. Markman nonetheless attempted to dismiss the ISAE problem of Emend® IV because there are allegedly various workarounds; however, the very need for such workarounds serves as "evidence of efforts to solve that problem." *See WBIP*, 829 F.3d at 1334 (noting that replacing the exhaust pipes in older generation gen-sets constituted evidence of efforts to solve the carbon monoxide poisoning problem and that the claimed invention solved a long-felt need in the industry). Diluting the fosaprepitant product, adding other antiemetics to the bag, and using a central line (if one is available) are all evidence of the industry's recognition of, and efforts to solve, the problems with Emend® IV. TD2 729:20-731:18 (discussing workaround of diluting fosaprepitant did not have label support) (Markman); TD3 1045:17-1046:18 (discussing how combining antiemetics in the same bag is "not according to the label" and antiemetics are given sequentially), 1054:21-1057:21 (discussing how a central line is not always available and is only put in to facilitate cancer treatment) (Roeland); *see also* TD2 710:10-12 (Markman) (Markman agrees not all patients who are given chemotherapy have central lines). In fact, Dr. Markman affirmed that one study diluted the fosaprepitant product and administered the drug over a longer period of time to "overcome a problem they saw," which was the ISAEs with the fosaprepitant product. *See* DTX-35.1, TD2 730:14-731:18 (Markman).

Industry evidence thus shows that there was a need for an intravenous NK-1 receptor antagonist that was safe (*i.e.*, with fewer side effects) and effective.[23] *See* TD3 1058:17-1059:2 (Roeland). Heron's Cinvanti® resolved that need as it is "equally as efficacious and had fewer related infusion site reactions," which is attributed to the fact that it is polysorbate 80-free. TD3 1060:9-1061:2, 1064:13-1065:16 (Roeland) (discussing JTX-126 that details one of the reasons for the reduced frequency of ISAEs with Cinvanti® is the elimination of polysorbate 80). This better safety profile is further shown by juxtaposing the Emend® IV and Cinvanti® labels, in which the former has an ISAE warning that the latter does not. *Compare* JTX-129 *with* JTX-51; *see also* TD3 1066:5-18 (Roeland).

2. Failure of Others

"Longfelt need is closely related to the failure of others. Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *In re Cyclobenzaprine*, 676 F.3d at 1082. For more than 20 years following Merck's discovery of aprepitant, no successful intravenous aprepitant formulation had been developed until Heron invented Cinvanti®. TD3 955:10-956:5 (Hale); TD4 1322:21-1323:21 (Little). Cinvanti® remains the first and only intravenous aprepitant product approved by the FDA. TD4 1347:22-1348:13 (Little).

"[W]hen the evidence indicates that others found development of the claimed invention difficult and failed to achieve any success . . . evidence of failed attempts by others could be determinative on the issue of obviousness." *In re Cyclobenzaprine*, 676 F.3d at 1081. Merck,

[23] To the extent Fresenius argues CN '845 satisfied this need in the art because it is an aprepitant emulsion without polysorbate 80, this is incorrect. Fresenius has not met its burden to show that any CN '845 emulsion was stable or could be given to patients (*supra* §§ II.C.2 and IV.E.2), nor were the CN '845 emulsions FDA approved or commercially available (TD2 595:3-6 (Markman)).

among other sophisticated companies, failed to develop an intravenous aprepitant drug product by overcoming challenges associated with aprepitant's low solubility. TD3 955:10-956:5 (Hale); TD4 1322:21-1323:21 (Little). Aprepitant has characteristics of "cement dust" with high crystallinity and low solubility, and because of aprepitant's poor physical characteristics, an intravenous formulation of aprepitant was considered impossible. PTX-3.1 ("The sparing water solubility of [aprepitant] precludes its formulation in a vehicle acceptable for intravenous administration in humans."); TD3 900:10-22, 901:17-902:5, 910:9-911:23 (Hale).

"Evidence that others were going in different ways is strong evidence that the inventor's way would not have been obvious." *See In re Cyclobenzaprine*, 676 F.3d at 1082. Merck investigated multiple alternatives to an intravenous formulation of aprepitant, but achieved success only with aprepitant's prodrug fosaprepitant. TD3 942:4-19 (Hale); TD4 1347:22-1348:13 (Little). Though fosaprepitant was a successful intravenous NK-1 receptor antagonist formulation, it represented Merck's failure to develop an actual intravenous formulation of aprepitant. TD1 1347:22-1348:1 (Little). Additionally, many other sophisticated pharmaceutical companies chose to try to develop entirely new NK-1 receptor antagonists rather than work with aprepitant. *See* TD3 944:6-945:11 (Hale); PTX-13.22.

No pharmaceutical company besides Heron successfully developed an intravenous aprepitant formulation. TD3 955:23-956:5 (Hale); TD4 1322:21-1323:21 (Little). There is no evidence that the researchers behind CN '845 and Zhou were able to successfully develop a viable product from their unstable aprepitant formulations, even though that was their goal. *See* JTX-71; JTX-115; *supra* § II.C.2. Indeed, Hingorani stated that "to the best of [its] inventors' knowledge, no such soluble and stable formulation of aprepitant has been reported." JTX-21.2. These real-world failures of others, including any failure to obtain FDA approval, support a finding of

nonobviousness. *See Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (reversing district court for not viewing evidence of competitors' failure to obtain FDA approval in light most favorable to patentee).

As of September 2014, any attempt to develop an intravenous aprepitant product was considered a failure. *See* TD3 954:3-13 ("[I]ntravenous aprepitant . . . didn't exist. So it's a failure. So I think looking at the efforts at Merck, efforts from other people to identify new molecules that weren't aprepitant, it indicated that they too failed and moved on . . . to get to what is really the goal here, an NK-1 antagonist for intravenous use.") (Hale). Indeed, Dr. Hale concluded that Heron's development of Cinvanti® "cracked this problem that [Merck or anyone else was not] able to solve," in the 20 previous years, having a reaction of "[s]urprising, but kudos, good job," when he heard the news. TD3 955:23-956:5 (Hale).

3. Unexpected Results

Unexpected results can be demonstrated when "the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). In other words, "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results."); *Leo Pharm.*, 726 F.3d at 1358 ("Unexpected properties are useful to show the improved properties provided by the claimed [product] are much greater than would have been predicted.").

A POSA would have had no expectation that a physically stable intravenous aprepitant emulsion formulation could be made and used safely. Intravenous emulsion formulations were reported in the prior art to be difficult to develop, and the prior art attempts at developing an

intravenous aprepitant emulsion were not successful. *See* TD4 1344:20-1345:19 (Little); TD3 914:18-919:1 (Hale). Neither CN ’845 nor Zhou provided data demonstrating adequate physical stability, and both Examples 4 and 5 of the patents-in-suit, which were based on CN ’845 and Zhou, formed crystals within four days. *See* TD4 1246:15-1247:4, 1269:12-1270:1, 1345:3-19 (Little).

The difference in stability between Cinvanti® and Examples 4 and 5 is a “difference in kind.” *See* TD4 1346:10-14 (Little). Cinvanti® is “suitable for long-term stability so that they’re able to be utilized [and] they’re able to be commercialized,” whereas the formulations in the prior art shown in Examples 4 and 5 were not stable for even four days. *See* TD4 1345:24-1346:15, 1347:1-5 (Little); *see also* TD2 541:23-542:7 (Ottobani) (if a formulation is not stable for one week “it becomes almost impossible to commercialize”).

The properties of the claimed aprepitant emulsion formulations also were safe for administration through IV push, which is a faster delivery method than other IV NK-1 receptor antagonists. This delivery option reduces preparation and administration time for nurses and pharmacists, reduces the use of infusion supplies, and reduces the time required for patient treatment, allowing clinicians to provide cancer therapy to more patients every day. *See* TD3 1067:19-1069:23 (provides efficiency and saves nurses time), 1070:19-1071:15 (saves patients time), 1071:16-1074:19 (publication shows intravenous push saves institutions time) (citing JTX-155), 1077:3-20 (“the two-minute IV push matters . . . and the nursing staff and the pharmacists are very clear that they will not be going back to a 20 or 30-minute IV infusion.”) (Roeland).

4. Commercial Success

“[T]he law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art.” *Integra Lifesciences Corp. v. HyperBranch Med. Tech. Inc.*, No. 15-819-LPS-CJB, at *23 (D. Del. Apr.

20, 2018) (citing *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005)); *see also J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). "When a patentee can demonstrate commercial success . . . , and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *Id.* Cinvanti® is a commercial success. TD4 1177:13-1178:1 (Tate).

In determining whether a marketed product is commercially successful, courts may look at the total sales of the product and market share since its introduction to the relevant market. *See, e.g.*, *Neupak, Inc. v. Ideal Mfg. & Sales Corp.*, 41 F. App'x 435, 440 (Fed. Cir. 2002) (noting sales figures with market data provide strong evidence of commercial success); *In re Alfuzosin Hydrochloride Patent Litig*, No. 08-1941, 2010 WL 1956287, at *7 (D. Del. May 14, 2010) (commercial success where there were 1.8 million prescriptions and total sales of drug were $790 million after six years on market and growing). Cinvanti® has demonstrated significant sales and maintained significant market share[24], even in the face of competition from a product that was considered the gold standard for 10 years (Emend® IV) and generic competition. From launch in January 2018 through June 2023, 3.1 million units of Cinvanti® were sold for a total of $484 million. TD4 1144:13-18 (Tate); TD3 862:18-21 (Masztak); JTX-181.1. From launch in 2018 through the end of Quarter 3, 2019, Cinvanti®'s market share grew period over period and rose to about 43%. TD4 1158:9-13 (Tate); TD3 863:24-864:4 (Masztak). In September 2019, generic fosaprepitant entered the market, and following a decline during the six-quarter arbitrage, Cinvanti®'s market share stabilized in the range of 25% to 28%. TD4 1158:16-25 (Tate); TD3 861:24-862:5 (Masztak) (agreeing with Tate's aggregation); TD3 797:20-24, 798:18-23, 799:11-

[24] There is no dispute that Cinvanti®'s economic market is intravenous NK-1 receptor antagonists. *See* TD3 863:9-13 (Masztak); TD4 1155:13-1157:7, 1157:16-1158:8 (Tate).

800:10 (Sullivan); PTX-25. That Cinvanti® has demonstrated commercial success "despite being a late entrant and in the face of significant generic competition provides further confirmation of [that patented drug's] success in the marketplace." *Vifor Fresenius Med. Care Renal Pharma Ltd. v. Teva Pharm. USA, Inc.*, 623 F.Supp.3d 389, 411 (D. Del. 2022).

Cinvanti®'s commercial success is attributable to the benefits of its formulation as claimed in the patents-in-suit. Cinvanti®'s formulation is polysorbate 80-free and can be given as a two-minute intravenous push.[25] *See* TD3 770:1-11 (Sullivan). Cinvanti® is also in a ready-made vial, meaning it does not need to be reconstituted (*i.e.*, mixed up) and can be stored at room temperature for 60 days. *See* TD3 1068:9-1069:1 ("[P]harmacists don't have to mix it up, the nurses can . . . inject it over two minutes right with the patient.") (Roeland); TD3 779:3-9 (can be stored at 60 days at room temperature) (Sullivan). These benefits, which are properties of the formulation, differentiated Cinvanti® in the marketplace from its competitors.[26] *See* TD3 778:15-779:9, 802:8-803:4 (Sullivan); TD4 1167:20-1170:2, 1172:21-1173:1 (Tate) (citing DTX-265.10).

5. Copying

Evidence of copying is a "respected source[] of objective evidence of nonobviousness." *See, e.g.*, *Ortho-McNeil Pharm. v. Mylan Lab'ys., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008); *see also Ortho-McNeil Pharm. v, Mylan Lab'ys.*, 348 F.Supp.2d 713, 759 (N.D.W. Va. 2004) ("[T]he

[25] Fresenius's expert, Dr. Markman, questions the value of the two-minute IV push. *See* TD2 674:13-17 (Markman). Heron, however, presented evidence of its value to clinicians and patients. *See* TD4 1174:19-1175:3 (Tate) (about half of survey participants used Cinvanti® as a push); *see also* JTX-169.59. Dr. Roeland also relayed his experience with the two-minute push and how it has impacted his patients and institution. *See* TD3 1067:19-1069:23 (provides efficiency and saves nurses time), 1070:19-1071:15 (saves patients time), 1071:16-1074:19 (publication shows IV push saves institutions time), 1077:3-20 ("the nursing staff and the pharmacists are very clear that they will not be going back to a 20 or 30-minute IV infusion.") (Roeland).

[26] Fresenius recognized that Cinvanti® is "doing exceedingly well in the market" and it is a product they "really like," highlighting the same Cinvanti® benefits discussed above as motivation to develop a generic and a strategic fit for its business.[26] *See* DTX-304.3; JTX-184.1; JTX-186.5.

Court finds that [a generic drug manufacturer]'s decision to copy [one product] instead of [another] is significant evidence of non-obviousness."). Although evidence of copying required by the Hatch-Waxman Act is not considered probative in the ANDA context, copying of claim elements that the Hatch-Waxman Act does not require is relevant to nonobviousness. *See Dey, L.P. v. Teva Parenteral Medicines, Inc.*, 6 F.Supp.3d 651, 681 (N.D.W. Va. 2014), *aff'd*, 600 F. App'x 773 (Fed. Cir. 2015) (copying by a generic, where there is no regulatory requirement to do so, "provides a strong indication that the prior art provided Teva with no obvious alternative to [the] invention"); *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc., USA*, No. 07-CV-5855 DMC-JAD, 2011 WL 383861, at *9 (D.N.J. Feb. 3, 2011) (same).

Fresenius could have filed a 505(b)(2) application in which it changed the formulation compared to Cinvanti®, yet decided not to. *See* TD2 403:12-404:20 (Rabinow). If Dr. Rabinow's theories were correct, Fresenius could have copied CN '845 or Zhou. Instead, Fresenius represented to the FDA that its product is a "direct copy of Cinvanti®." *See* JTX-26.10; JTX-36.1; JTX-43.2; JTX-192; JTX-193.2.[27] Fresenius selected Heron's formulation of ingredients and amounts claimed in the patents-in-suit because they were significant, and that evidence of copying reinforces nonobviousness.

6. There Is a Nexus Between the Claimed Invention and Cinvanti®

Each of the objective indicia discussed above are tied to the properties of the Cinvanti® formulation. Cinvanti® is Heron's commercial embodiment of the invention of the patent-in-suit. *See* TD4 1340:14-22 (Little). Because the formulation and use of Cinvanti® embodies the invention, a "nexus" exists to the patented subject matter—*i.e.*, there is a relationship between the

[27] Fresenius's scientists even acknowledged that they were in the "best position[] to *copy*" Cinvanti®. JTX-184.1.

claimed subject matter of the patent and the particular objective indicia. *See, e.g.*, *WBIP*, 829 F.3d at 1329-30 ("[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product is the invention disclosed and claimed in the patent.") (citations and quotations omitted).

Moreover, Heron also affirmatively showed that the objective indicia are attributable to the claimed formulation. *See* TD3 770:1-11 (discussing polysorbate 80-free and two-minute intravenous push) (Sullivan); TD3 1060:9-1061:2 (Cinvanti® is equally efficacious with fewer ISAEs), 1064:5-1065:16 (reduced ISAEs due to elimination of polysorbate 80 in Cinvanti®) (Roeland); TD4 1340:14-1343:5 (Cinvanti® is an embodiment of the Asserted Claims) (Little). And Fresenius has not shown otherwise. *See, e.g., Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1393 (Fed. Cir. 1988) ("When the patentee has presented a prima facie case of nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger . . . .").

V. Fresenius Failed to Prove The Asserted Claims Invalid Under 35 U.S.C. § 112

A. Fresenius Failed to Prove That Heron Did Not Possess the Claimed pH Range of 7.5 to 9.0

In a brief moment of direct testimony, Dr. Rabinow offered his opinion about written description, saying that the patent fails to have written description support because "the examples that were alleged to be found to be viable, stable formulations was all done in a very narrow pH range of something like 8.7 to 8.8." TD1 306:25-307:3 (Rabinow). This is wrong. The specification is not required to have actual examples of every embodiment claimed. *See Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) ("[E]xamples are not necessary to support the adequacy of a written description."). Rather, it needs to "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1136

(Fed. Cir. 2018) (citation omitted).

The claimed pH range of 7.5-9.0 is expressly disclosed in the patent specification. JTX-1.8 (4:65-67). Further, the inventive examples all use a pH in this claimed range while demonstrating stability over a long period of time. JTX-1.14-17 (16:1-18:13, 19:28-21:10). Moreover, this pH range worked for the formulations of both Cinvanti® and Fresenius's ANDA Products. *See* TD4 1352:7-1353:7 (Little); *see also* TD1 16:15-23, 19:15-22, 24:17-25:4 (Little); JTX-33.1; JTX-47.2.

B. Fresenius Failed to Prove That Heron Did Not Possess the Claimed Treatment Regimen in Claim 21 of the '229 Patent

Fresenius also attempts to challenge the validity of claim 21 of the '229 patent as not showing possession of the claimed treatment regimen because the specification of the patents-in-suit lack clinical studies. TD2 596:12-23 (Markman). This argument is incorrect—it goes against the state of the art and also ignores the pharmacokinetic data from *in vivo* animal models using aprepitant, which was an active ingredient with established clinical efficacy. JTX-1.17 (21:35-22:41); *see also* TD2 594:20-595:14, 596:4-11, 699:1-22 (Markman).

VI. Conclusion

For at least the reasons stated at trial and set forth above, the Court should issue judgment for Heron on claims 9, 10, and 21 of the '229 patent and claims 9 and 10 of the '794 patent.

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CERTIFICATE OF SERVICE

I hereby certify that on July 30, 2024, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on July 30, 2024, upon the following in the manner indicated:

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